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PART II

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

■

FOOD FOR HUMAN CONSUMPTION

Additives and GRAS Substances

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER B—FOOD AND FOOD PRODUCTS

PART 121—FOOD ADDITIVES

Amino Acids in Food for Human Consumption

Conditions of Safe Use in Food and Deletion from GRAS List

A proposal was published in the Federal Register of April 6, 1972 (37 FR 6938) to establish the conditions for safe use for amino acids used to improve the protein value of food, and to delete amino acids for nutritive purposes in the human diet from the GRAS list, § 121.101(d)(5) (21 CFR 121.101).

Uncontrolled uses of amino acids in the fortification of certain foods may result in risk to the public health from excessive intakes of free amino acids. Studies on experimental animals have shown that excessive intake of amino acids and amino acid imbalance can include growth retardation and degeneration of certain organs which can lead to the animals' early death. On the other hand, properly controlled additions of the amino acid(s) to appropriate protein-containing foods can benefit the consumer by improving the biological quality of the proteins.

Thirty-nine comments were received on the proposal. Twenty-eight comments were from manufacturers or associations of manufacturers that either produce amino acids or foods in which amino acids are used, or both. Nine comments were from professional scientists in health and allied fields associated with governmental or non-profit organizations, institutions, and associations. One comment was received from a medical group and one was received from a public interest group.

The principal comments raised and the Commissioners' conclusions thereon are as follows:

Appropriateness of the Limitations For Use of Amino Acids

1. A number of comments discussed the requirement that the finished food to which the amino acids are added should furnish at least 6.5 grams of intact protein per day. Many objected to this on the basis that there are a number of foods to which the addition of Amino acids will produce some benefit, but which supply less than 6.5 grams of intact protein per day. Some comments stated that since the nutrition labeling proposal published in the Federal Register on March 30, 1972 (37 FR 6493) considered a level of 5 percent of the U.S. Recommended Daily Allowance (3.25 grams) to provide a significant contribution of nutrients for nutrition labeling purposes, this lower figure should apply to this regulation as well.

The Commissioner recognizes that the proper addition of amino acids to a food may improve the nutritional quality thereof. In order that the fortification of foods be truly significant in relation to the diet of the United States consumer, it is concluded that amino acid fortification should be permitted for only those foods containing at least 10 percent of the U.S. Recommended Daily Allowance (U.S. RDA) of protein, which is 65 grams per day for adults, § 1.17(c)(7)(ii)(a) (21 CFR 1.17). There is no merit in the contention that a level of 5 percent should be adopted merely on the basis that such a nutrient level was proposed for the cutoff point above which nutrition labeling could be used since that level related to significance on a serving basis only and not to the daily intake. The nutrition labeling regulations require a level of 10 percent of the U.S. RDA for any claim of nutritional significance or superiority, § 1.17(c)(v).

2. Two comments requested clarification of the term "intact protein" as used in the proposal. Another suggested modification to permit supplementation of partially hydrolyzed protein.

The Commissioner concludes that revision of the wording to limit the addition of amino acids to "foods containing primarily-intact naturally occurring protein" will clarify this provision. This language is adopted to eliminate the possibility of adding amino acids to foods containing no protein but to permit the fortification of foods where some of the original protein may have been hydrolyzed.

3. A number of objections were made to the requirement that the protein efficiency ratio (PER) of the food to be supplemented must be less than 2.5, i.e., less than 100 percent of the adjusted PER of casein, and to the requirement that the PER of an amino acid supplemented food in its finished form must be 2.5 or more. Other comments stated that such restrictions would prevent the addition of amino acids to improve foods containing good quality protein, even though a PER of 2.5 could not be reached. These comments also pointed out that in placing the minimum for improvement of the finished food so high, undue emphasis was placed on meat, milk, and eggs as the preferred protein sources in the diet. Arguments were also advanced that, since cereal grains are a common and good protein source in many diets, particularly in other countries, supplementation of such foods should be provided for by permitting fortification to a minimum PER of 2.0 (80 percent of casein).

The Commissioner has concluded that there is no reason to permit amino acid supplementation unless it will provide for a significant improvement in the protein quality. Exceptions to the PER limitation of 100 percent of casein will be considered separately on a case by case basis upon receipt of a petition therefor, providing that the minimum level requested is not less than 80 percent of casein.

It is also concluded that there is no reason to restrict fortification of a food already containing an original PER of 2.5 or more, if such fortification will provide a significant increase ((P) value of less than 0.05) in the original PER. Since the PER test is a biological value test, a statistically significant improvement in the protein quality will provide a nutritionally significant improvement.

4. Other objections raised the issue that the requirement of a PER increase of 0.25 for each added amino acid is too severe and should be dropped. Some did not quarrel with the 0.25 requirement but pointed out that two or more amino acids may be needed in combination to attain the 0.25 increase. One comment suggested that it would be preferable to measure the value of any addition of amino acid(s) by determining if the resultant PER showed an increase over the PER of the naturally occurring intact protein by an amount statistically significant with a probability (P) value of less than 0.05.

The Commissioner recognizes the need to prevent random addition of amino acids to food. He also recognizes the fact that, in some protein sources, there may be more than one limiting amino acid needed in combination to produce a significant increase in the PER. Accordingly, the Commissioner has concluded to retain the requirement that a significant increase in PER be reached if any addition of amino acids is made. He also concludes that a combination of two or more amino acids should be permitted to achieve the significant increase if a lesser number of amino acids cannot produce the required increase. A statistically significant increase in the PER, which will provide a nutritionally significant improvement in the protein, should be required rather than a single numerical value since there may be situations when an increase of 0.25 PER by adding a limiting amino acid(s) may not be statistically significant at a (P) value of less than .05. A significant increase in the PER will aid in producing a significant source of protein contribution to the diet.

Adequacy of the Method for Measuring PER

Some comments questioned the use of casein as the reference standard and the use of the PER test for protein evaluation. One comment asked for clarification that the test is run isonitrogenously.

The use of casein as a reference standard in determining the PER of protein is in accordance with the method described in sections 39.166–39.170, "Official Methods of Analysis of the Association of Official Analytical Chemists," 11th Edition, 1970.[1] The method requires that the test be run isonitrogenously. A uniform supply of casein can be obtained, whereas a uniform source of other purified proteins such as lactalbumin and whole egg is not readily available. Casein has an acceptable essential amino acid pattern. The limitations of the PER test are recognized, but at this time it is the best method available and the

[1] Copies may be obtained from: Association of Official Analytical Chemists P. O. Box 540, Benjamin Franklin Station Washington, D. C. 20044

official method for regulatory purposes. It is pertinent to recognize that many of the protein foods or protein supplemented foods will be used by children and it is therefore appropriate to use an assay which employs a growing animal as the test subject. Accordingly, the Commissioner concludes that the method provided is an appropriate one at this time.

LIMITATION OF THE AMINO ACID ADDITION FOR NUTRITIVE USE ONLY

A number of manufacturers took issue with limiting the use of amino acids for nutritive purposes on the basis that use af amino acids for other purposes would no longer be permitted.

No action is being taken at this time to remove from GRAS classification other amino acids or their derivatives that have other than nutritive uses. Section 121.101(d)(5) has provided authority only for using the ingredients listed thereunder as nutrients and not for other uses. If amino acids are used for technological uses not covered in the published GRAS list or in other regulations it is possible to request concurrence therefor by submission of a petition to the Food and Drug Administration for GRAS affirmation pursuant to § 121.40.

LIMITATION OF ACCEPTABLE ISOMERS TO THE L-FORM OF AMINO ACIDS

There were contrasting views expressed on the use of the various isomeric forms (the natural L-form or the commercially available mixtures of DL-forms) of amino acids. Some felt that more consideration should be given to whether only L-isomers are acceptable, offering references to certain scientific studies purporting to show some usefulness of the DL-form. Others suggested that only L-isomers should be used until further studies are carried out on the effect of the DL-isomers on man.

Because of the substantial lack of information on the biological effectiveness and safety of the DL-isomers, the Commissioner concludes that the acceptable forms of the amino acids should be restricted to the L-form except for DL-methionine and for glycine. There is appreciably more understanding of the safety of DL-methionine added to foods than there is for the DL-forms of the other amino acids. DL-methionine has been investigated and found to be acceptable as long as it is not used in infant food. D-methionine ingestion by infants may lead to a methioninuria that may hinder the proper diagnosis of a disease condition. Although adults and children also exhibit methioninuria following D-methionine ingestion, the diagnostic significance of the amino acid in the urine is of much less relative importance. Glycine does not occur in an optically active form.

Petitions may be submitted to establish the safety and nutritional value of commercially available mixtures of DL-forms when the required supporting data become available.

ACCEPTABILITY OF ADDITIONAL FORMS OF AMINO ACIDS

A number of comments pointed out the safety and usefulness of the sodium and potassium salts and acetate and sulfate forms of the amino acids and L-asparagine and L-glutamine.

The Commissioner concludes that except for the acetate and sulfate forms, these are appropriate and are included in the final order. The acetate and sulfate forms have no history of safe use and may not be used prior to promulgation of a food additive regulation.

USE OF AMINO ACIDS IN FORMULATIONS OF SPECIAL FOODS FOR NUTRITIONAL USE IN MEDICAL CONDITIONS

Several comments raised the question whether the regulation should cover amino acids used in special foods for controlled diets.

Such foods are intended for use solely under medical supervision to meet nutritional requirements in specific medical conditions. The quality and usefulness of these products must be determined on an individual product basis because of special nutritional needs dictated by the pathophysiologic conditions of a particular patient. The amino acids used in such products must be safe and of food grade, but it is inappropriate that the limitations relating to the amino acid fortification of protein in regular diets apply to them. Accordingly, the Commissioner exempts these foods for special dietary use from certain provisions of the regulation set forth below. Such foods shall be subject to all of the applicable requirements of 21 CFR Part 125.

AMINO ACID CONTENT OF EGG PROTEIN AS BASIS FOR MAXIMUM USE LEVELS

Some comments claimed that the upper limit of amino acid addition should be based only upon the amount demonstrated to achieve the maximum PER value for a food protein.

The Commissioner concludes that it is in the best interest of the consumer to permit and encourage rational fortification of foods with amino acids by limiting permissible supplementation to a safe level. A standard protein with established safety was needed to establish such limits, preferably one with high biological quality. Egg protein has the highest biological quality of any naturally occurring protein. It is generally agreed that the relative amino acid composition of egg is an ideal pattern for nutritional value and the proportion of individual essential amino acids to total protein content is generally the highest of most protein-containing foods in common use.

ILLEGALITY OF THE PROPOSED REGULATION

A public interest group alleged that the proposed regulation is illegal on the ground that it does not comply with section 409 of the act.

The Commissioner concludes that promulgation of this regulation is in accord with his broad general responsibility for protection of the public health, and is specifically in accord with section 409 of the act and § 121.41 of the food additive regulations. This regulation is issued on the Commissioner's initiative pursuant to section 409(d) of the act. The Commissioner has concluded, on the basis of all of the scientific literature and other available information, that the amino acids have been shown by all appropriate methods to be safe under the conditions of use established in this regulation.

USE OF AMINO ACIDS FOR ANIMALS

Two firms raised questions about the status of amino acids used in animal feed if the proposed deletion from the GRAS list were accomplished.

Recognizing that amino acids are used in animal feeds and considering that the action taken herein is concerned with uses of amino acids in human food, the Commissioner concludes that the presently listed amino acids may remain on the existing GRAS list for animal feed until such time as a separate GRAS list for animal food ingredients is issued.

VARIATIONS IN ASSAY RESULTS

One comment suggested that a 10 percent excess over the allowable maximum amounts of individual amino acids should be permitted because of the variability in the assay methods available.

The Commissioner has considered the suggestion carefully and has concluded that there is no merit in providing for a 10 percent overage in the regulation. Any enforcement action that might be taken based on the maximum amounts of amino acids present would of necessity consider the variability of the method by which the amounts were determined.

LISTING OF ESSENTIAL AND NON-ESSENTIAL AMINO ACIDS

Several comments questioned the listing of nonessential amino acids with essential amino acids since the nonessential amino acids are usually thought not to improve the protein efficiency ratio.

The Commissioner recognizes that the addition of nonessential amino acids is unlikely to alter the PER. However, the total intake of non-specific nitrogen found in nonessential amino acids not only may have a sparing effect and thus influence the requirements of the essential amino acids, but also may provide properties important for foods used solely under medical supervision to meet nutritional requirements in specific medical conditions. Accordingly, the Commissioner concludes that it is inappropriate to separate the two classes of amino acids within the context of the regulation.

SPECIFICATIONS FOR AMINO ACIDS

Comments were received that certain amino acid specifications in both the Food Chemicals Codex and in NAS–NRC Publication No. 1344, referenced in the proposal are inappropriate.

Specifications in the latest edition of the Food Chemicals Codex are regarded by the Commissioner as the food grade specifications for food additives unless specifically stated to be otherwise in any given food additive regulation. Comments regarding a need for changes or

inclusions in these specifications should be adressed to the Codex. Specifications in NAS–NRC Publication No. 1344 are retained for the four amino acids not yet included in the Codex.

GENERAL

One scientist opposed the entire concept of amino acid fortification and stated that improvement of protein quality by fortification with free amino acids may create an imbalanced diet and undesirable effects on human physiology. The new regulation is designed to prevent such a situation by limiting the amounts, isomers, and combinations permitted, based upon the scientific evidence and the considered judgment of nutritional scientists.

The public interest group requested that the data necessary to demonstrate compliance with paragraph (d) of the regulation should be submitted to the Food and Drug Administration so that the public would be able to review it. The Commissioner concludes that, like other quality control records, it is sufficient that this data be retained at the company and available for inspection by the Food and Drug Administration. It would be impracticable and burdensome for every food manufacturer using amino acids to submit such data to the Food and Drug Administration.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1785–1788; 21 U.S.C. 321(s), 348, 371(a)) and under the authority delegated to the Commissioner (21 CFR 2.120), Part 121 is amended as follows:

§ 121.101 [Amended]

1. In subparagraph (5) of § 121.101(d) in the "Limitations, restrictions or explanations" column by adding the text "Food additive regulation § 121.1002" for the following amino acids:

Product	Tolerance	Limitations, restrictions or explanations
• • •	• • •	• • •
(5) NUTRIENTS AND/OR DIETARY SUPPLEMENTS [1]		
Alanine (L- and DL-forms)		Food additive regulation § 121.1002.
Arginine (L- and DL-forms)		Do.
• • •	• • •	• • •
Aspartic acid (L- and DL- forms)		Food additive regulation § 121.1002.
• • •	• • •	• • •
Cysteine (L-forms)		Food additive regulation § 121.1002.
Cystine (L- and DL-forms)		Do.
• • •	• • •	• • •
Histidine (L- and DL-forms)		Food additive regulation § 121.1002.
• • •	• • •	• • •
Isoleucine (L- and DL-forms)		Food additive regulation § 121.1002.
Leucine (L- and DL-forms)		Do.
• • •	• • •	• • •
Lysine (L- and DL-forms)		Food additive regulation § 121.1002.
• • •	• • •	• • •
Phenylalanine (L- and DL-forms)		Food additive regulation § 121.1002.
• • •	• • •	• • •
Proline (L- and DL-forms)		Food additive regulation § 121.1002.
• • •	• • •	• • •
Serine (L- and DL-forms)		Food additive regulation § 121.1002.
• • •	• • •	• • •
Threonine (L- and DL-forms)		Food additive regulation § 121.1002.
• • •	• • •	• • •
Tryptophane (L- and DL-forms)		Food additive regulation § 121.1002.
Tyrosine (L- and DL-forms)		Do.
Valine (L- and DL-forms)		Do.

[1] Amino acids listed may be free, hydrochloride salt, hydrated, or anhydrous form, where applicable.

2. By adding a new section to Subpart D, to read as follows:

§ 121.1002 Amino acids.

The food additive amino acids may be safely used as nutrients added to foods in accordance with the following conditions:

(a) The food additive consists of one or more of the following individual amino acids in the free, hydrated or anhydrous form or as the hydrochloride, sodium or potassium salts:

L-Alanine
L-Arginine
L-Asparagine
L-Aspartic acid
L-Cysteine
L-Cystine
L-Glutamic acid
L-Glutamine
Glycine
L-Histidine
L-Isoleucine
L-Leucine
L-Lysine
DL-Methionine (not for infant foods)
L-Methionine
L-Phenylalanine
L-Proline
L-Serine
L-Threonine
L-Tryptophan
L-Tyrosine
L-Valine

(b) The food additive meets the following specifications:

(1) As found in "Food Chemicals Codex," National Academy of Sciences-National Research Council (NAS–NRC), 2nd Edition (1972)[3] for the following:

L-Alanine
L-Arginine
L-Arginine Monohydrochloride
L-Cysteine Monohydrochloride
L-Cystine
Glycine
L-Leucine
DL-Methionine
L-Methionine
L-Tryptophan
L-Phenylalanine
L-Proline
L-Serine
L-Threonine
Glutamic Acid Hydrochloride
L-Isoleucine
L-Lysine Monohydrochloride
Monopotassium L-glutamate
L-Tyrosine
L-Valine

(2) As found in "Specifications and Criteria for Biochemical Compounds," NAS–NRC Publication, 3rd Edition (1972)[3] for the following:

L-Asparagine
L-Aspartic acid
L-Glutamine
L-Histidine

(c) The additive(s) is used or intended for use to significantly improve the biological quality of the total protein in a food containing naturally occurring primarily-intact protein that is considered a significant dietary protein source, provided that:

(1) A reasonable daily adult intake of the finished food furnishes at least 6.5 grams of naturally occurring primarily intact protein (based upon 10 percent of the daily allowance for the "reference" adult male recommended by the National Academy of Sciences in "Recommended Dietary Allowances," NAS Publication No. 1694, 7th Edition (1968)).[4]

(2) The additive(s) results in a protein efficiency ratio (PER) of protein in the finished ready-to-eat food equivalent to casein as determined by the method specified in paragraph (d) of this section.

(3) Each amino acid (or combination of the minimum number necessary to achieve a statistically significant increase) added results in a statistically significant increase in the PER as determined by the method described in paragraph (d) of this section. The minimum amount of the amino acid(s) to achieve the desired effect must be used and the increase in PER over the primarily-intact naturally occurring protein in the food must be substantiated as a statistically significant difference with at least a probability (P) value of less than 0.05.

(4) The amount of the additive added for nutritive purposes plus the amount naturally present in free and combined (as protein) form does not exceed the following levels of amino acids expressed as percent by weight of the total protein of the finished food:

[3] Copies may be obtained from: National Academy of Sciences 2101 Constitution Avenue, N.W. Washington, D.C. 20037

[3] Copies may be obtained from: National Academy of Sciences, 2101 Constitution Avenue, N.W., Washington, D.C. 20037.

[4] National Academy of Sciences, 2101 Constitution Avenue, N.W., Washington, D.C. 20037.

	Percent by weight of total protein (expressed as free amino acid)
L-Alanine	6.1
L-Arginine	6.6
L-Aspartic acid (including L-asparagine)	7.0
L-Cystine (including L-cysteine)	2.3
L-Glutamic acid (including L-glutamine)	12.4
Glycine	3.5
L-Histidine	2.4
L-Isoleucine	6.6
L-Leucine	8.8
L-Lysine	6.4
L- and DL-Methionine	3.1
L-Phenylalanine	5.8
L-Proline	4.2
L-Serine	8.4
L-Threonine	5.0
L-Tryptophan	1.6
L-Tyrosine	4.3
L-Valine	7.4

(d) Compliance with the limitations concerning PER under paragraph (c) of this section shall be determined by the method described in sections 39.166–39.170, "Official Methods of Analysis of the Association of Official Analytical Chemists," 11th Edition, (1970).[3] Each manufacturer or person employing the additive(s) under the provisions of this section shall keep and maintain throughout the period of his use of the additive(s) and for a minimum of 3 years thereafter, records of the tests required by this paragraph and other records required to assure effectiveness and compliance with this regulation and shall make such records available upon request at all reasonable hours by any officer or employee of the Food and Drug Administration, or any other officer or employee acting on behalf of the Secretary of Health, Education, and Welfare and shall permit such officer or employee to conduct such inventories of raw and finished materials on hand as he deems necessary and otherwise to check the correctness of such records.

(e) To assure safe use of the additive, the label and labeling of the additive and any premix thereof shall bear, in addition to the other information required by the act, the following:

(1) The name of the amino acid(s) contained therein including the specific optical and chemical form.

(2) The amounts of each amino acid contained in any mixture.

(3) Adequate directions for use to provide a finished food meeting the limitations prescribed by paragraph (c) of this section.

(f) The food additive amino acids added as nutrients to special dietary foods that are intended for use solely under medical supervision to meet nutritional requirements in specific medical conditions and comply with the requirements of Part 125 of this chapter are exempt from the limitations in paragraphs (c) and (d) of this section and may be used in such foods at levels not to exceed good manufacturing practices.

Any person who will be adversely affected by the foregoing order may at any time on or before August 27, 1973, file with the Hearing Clerk, Food and Drug Administration, Rm. 6–88, 5600 Fishers Lane, Rockville, MD 20852, written objections thereto. Objections shall show wherein the person filing will be adversely affected by the order, specify with particularity the provisions of the order deemed objectionable, and state the grounds for the objections. If a hearing is requested, the objections shall state the issues for the hearing, shall be supported by grounds, factually and legally sufficient to justify the relief sought, and shall include a detailed description and analysis of the factual information intended to be presented in support of the objections in the event that a hearing is held. Objections may be accompanied by a memorandum or brief in support thereof. Six copies of all documents shall be filed. Received objections may be seen in the above office during working hours, Monday through Friday.

Effective date. Compliance with this order may begin immediately. This order shall be effective on January 23, 1974.

(Secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1785–1788; 21 U.S.C. 321(s), 348, 371 (a)).

Dated: July 19, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73–15211 Filed 7–25–73;8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 3, 121]

SUBSTANCES PROHIBITED FROM USE IN FOOD

Notice of Proposed Rulemaking

The Food and Drug Administration has prohibited the use of various substances in food on the basis of toxicological data showing a potential hazard to public health or because inadequate data exist to conclude that they are safe for use in food. Some of these actions were taken prior to enactment of the Food Additives Amendment of 1958, and others have been taken pursuant to that Amendment.

Because information on these actions is presently scattered throughout existing regulations, FEDERAL REGISTER notices not codified in the Code of Federal Regulations, old trade correspondence (TC), and unpublished correspondence, and thus are either difficult to find or are not generally available to the public, the Commissioner of Food and Drugs has concluded that they should be consolidated in one regulation. All of the substances presently proposed for inclusion in this regulation were the subject of action previously taken. The Commissioner is not now proposing such action against any additional substances. Should the current review of the safety of direct human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction justify additional action of this type, this proposed new section will also be used for that purpose.

Some of these food additives were prohibited from use in food on the conclusion that the available evidence did not establish safety, and not on the basis of a determination that the ingredient was in fact unsafe. Section 409 of the act places the burden on the manufacturer or distributor of a food additive to prove its safety prior to use. Accordingly, the Commissioner recognizes that, as additional scientific information becomes available, it may well be possible to approve one or more of these ingredients for food use and thus to delete it from this section. The proposed regulation provides for such transfers to and from this section on the Commissioner's initiative or on the petition of any interested person.

The fact that a substance does not appear on this list of prohibited substances does not mean that it may lawfully be used in food. This proposed new section includes only a partial list of prohibited substances, for easy reference purposes, and is not a complete list of substances that may not lawfully be used in food. Before any substance may be used in food, it must meet all of the applicable requirements of section 401 and 409 of the act.

Accordingly, the Commissioner of Food and Drugs concludes that it is in the public interest and will promote efficient enforcement of the act to provide a section in the food additive regulations to contain a listing of food ingredients for which use in food has been prohibited.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1785–1787, as amended; 21 U.S.C. 321(s), 348, 371(a)) and under authority delegated to him (21 CFR 2.120) the Commissioner proposes that Trade Correspondence No. 377 (December 29, 1941) be revoked, and that Title 21 of the Code of Federal Regulations be amended as follows:

§§ 3.14, 3.33 and 3.65 [Revoked]

1. That Part 3 be amended by revoking §§ 3.14, 3.33 and 3.65.

2. That Part 121 be amended by adding the following new section:

§ 121.106 Substances prohibited from use in food.

(a) The food ingredients listed in this section have been prohibited from use in food by the Food and Drug Administration because of a determination that they present a potential risk to the public health or have not been shown by adequate scientific data to be safe for use in food. Use of any of these substances in violation of this section causes the food involved to be adulterated in violation of the act.

(b) This section includes only a partial list of substances prohibited from use in food, for easy reference purposes, and is not a complete list of substances that may not lawfully be used in food. No substance may be used in food unless it meets all applicable requirements of the act.

(c) The Commissioner of Food and Drugs, either on his own initiative or on behalf of any interested person who has submitted a petition, may publish a proposal to establish, amend, or repeal a regulation under this section on the basis of new scientific evaluation or information. Any such petition shall include an adequate scientific basis to support the petition, shall be in the form set forth in § 2.65 of this chapter, and will be published for comment if it contains reasonable grounds.

(d) Substances prohibited from direct addition to food:

(1) *Calamus, oil of calamus, extract of calamus.* (i) Calamus is the dried rhizome of Acorus calamus L. It has been used as a flavoring compound, especially as the oil or extract.

(ii) Food containing any added calamus, oil of calamus, or extract of calamus is deemed to be adulterated in violation of the act based upon an order published in the FEDERAL REGISTER of May 9, 1968 (33 FR 6967).

(iii) The analytical method used for detecting oil of calamus (β-asarone) is in "Journal of the Association of Official Analytical Chemists" vol. 56, No. 5 (Sept. 1973).[1]

(2) *Dulcin.* (i) Dulcin is the chemical 4-ethyoxyphenylurea, $C_9H_{12}N_2O_2$. It is a synthetic chemical having a sweet taste about 250 times that of sucrose, is not found in natural products at levels detectable by the official methodology, and has been proposed for use as an artificial sweetener.

(ii) Food containing any added or detectable level of dulcin is deemed to be adulterated in violation of the act based upon an order published in the FEDERAL REGISTER of January 19, 1950 (15 FR 321).

(iii) The analytical methods used for detectine dulcin in food are in §§ 20.133 through 20.136 of the "Official Methods of Analysis of the Association of Official Analytical Chemists."[1]

(3) *P–4000.* (i) P–4000 is the chemical 5-nitro-2-n-propoxyaniline, $C_9H_{12}N_2O_3$. It is a synthetic chemical having a sweet taste about 4000 times that of sucrose, is not found in natural products at levels detectable by the official methodology, and has been proposed for use as an artificial sweetener.

(ii) Food containing any added or detectable level of P–4000 is deemed to be adulterated in violation of the act based upon an order published in the FEDERAL REGISTER of January 19, 1950 (15 FR 321).

(iii) The analytical methods used for detecting P–4000 in food are in §§ 20.137 through 20.141 of the "Official Methods of Analysis of the Association of Official Analytical Chemists."[1]

(4) *Coumarin.* (i) Coumarin is the chemical 1,2-benzopyrone $C_9H_6O_2$. It is found in tonka beans and extract of tonka beans, among other natural sources, and is also synthesized. It has been used as a flavoring compound.

(ii) Food containing any added coumarin as such or as a constituent of tonka beans or tonka extract is deemed to be adulterated under the act based upon an order published in the FEDERAL REGISTER of March 5, 1953 (19 FR 1239).

(iii) The analytical methods used for detecting coumarin in food are in §§ 19.104 through 19.023 of the "Official Methods of Analysis of the Association of Official Analytical Chemists."[1]

(5) *Cyclamate; calcium, sodium, magnesium and potassium.* (i) Calcium, sodium, magnesium and potassium salts of cyclohexane sulfamic acid, $(C_6H_{12}NO_3S)_2$ Ca, $C_6H_{12}N$ NA NO_3S, $(C_6H_{12}NO_3S)_2$ Mg, and C_6H_{12} N K NO_3S. Cyclamates are synthetic chemicals having a sweet taste 30 to 40 times that of sucrose, are not found in natural products at levels detectable by the official methodology, and have been used as artificial sweeteners.

(ii) Food containing any added or detectable level of cyclamate is deemed adulterated in violation of the act based upon an order published in the FEDERAL REGISTER of October 21, 1969 (34 FR 17063).

(iii) The analytical methods used for detecting cyclamate in food are in §§ 20.127 through 20.132 of the "Official Methods of Analysis of the Association of Official Analytical Chemists."[1]

(6) *Safrole.* (i) Safrole is the chemical 4-allyl-1,2-methylene-dioxybenezene $C_{10}H_{10}O_2$. It is a natural constituent of the sassafras plant. Oil of sassafras is about

[1] Copies may be obtained from: Association of Official Analytical Chemists, P.O. Box 540, Benjamin Franklin Station, Washington, D.C. 20044.

80 percent safrole. Isosafrole and dihydrosafrole are derivatives of safrole, and have been used as flavors.

(ii) Food containing any added safrole, oil of sassafras, dihydrosafrole, or safrole or as a constituent of any food or extract is deemed to be adulterated in violation of the act based upon an order published in the FEDERAL REGISTER of December 3, 1960 (25 FR 12412).

(iii) The analytical method used for detecting safrole, isosafrole and dihydrosafrole is in "Journal of the Association of Official Analytical Chemists" vol. 54, pp. 900–902 (1971).[1]

(7) *Monochloroacetic acid.* (i) Monochloroacetic acid is the chemical chloroacetic acid $C_2H_3ClO_2$. It is a synthetic chemical not found in natural products, and has been proposed as a preservative in alcoholic and non-alcoholic beverages. Monochloroacetic acid is permitted in food package adhesives with an accepted migration level up to 10 ppb under § 121.2520. The official methods do not detect monochloroacetic acid at the 10 ppb. level.

(ii) Food containing any added or detectable level of monochloracetic acid is deemed adulterated in violation of the act based upon trade correspondence dated December 29, 1941 (TC–377).

(iii) The analytical methods used for detecting monochloroacetic acid in food are in §§ 20.057 through 20.062 of the "Official Methods of Analysis of the Association of Official Analytical Chemists."[1]

(8) *Thiourea.* (i) Thiourea is the chemical thiocarbamide CH_4N_2S. It is a synthetic chemical, is not found in natural products at levels detectably by the official methodology, and has been proposed as an antimycotic for use in dipping citrus.

(ii) Food containing any added or detectable level of thiourea is deemed to be adulterated under the act.

(iii) The analytical methods used for detecting thiourea are in §§ 20.099 through 20.100 of the "Official Methods of Analysis of the Association of Official Analytical Chemists."[1]

(9) *Cobaltous Salts; acetate, chloride and sulfate.* (i) Cobaltous salts are the chemicals $Co(C_4H_6O_4)$, $Co\ Cl_2$ and $Co\ So_4$. They have been used in fermented malt beverages as a foam stabilizer and to prevent "gushing".

(ii) Food containing any added cobaltous salts is deemed to be adulterated in violation of the act based upon an order published in the FEDERAL REGISTER of August 12, 1966 (31 FR 8788).

(10) *NDGA (Nordihydroguaiaretic acid).* (i) Nordihydroguaiaretic acid is the chemical 4,4(2.3-dimethyltetramethylene) dipyrocatechol $C_{18}H_{22}O_2$. It occurs naturally in the resinous exudates of certain plants. The commercial product, which is synthesized, has been used as an antioxidant in foods.

[1] See footnote 1 previous page.

(ii) Food containing any added NDGA is deemed to be adulterated in violation of the act based upon an order published in the FEDERAL REGISTER of April 11, 1968 (33 FR 5619).

(iii) The analytical method used for detecting NDGA in food is in § 20.0008 of the "Official Methods of Analysis of the Association of Official Analytical Chemists."[1]

(11) *DEPC (Diethylpyrocarbonate).* (i) Diethylpyrocarbonate is the chemical pyrocarbonic acid diethyl ester, $C_6H_{10}O_5$. It is a synthetic chemical not found in natural products at levels detectable by available methodology and has been used as a ferment inhibitor in alcoholic and non-alcoholic beverages.

(ii) Food containing any added or detectable level of DEPC is deemed adulterated in violation of the act based upon an order published in the FEDERAL REGISTER of August 2, 1972 (37 FR 15426).

(e) Substances prohibited from indirect addition to food through use in food contact surfaces:

(1) *Flectol H.* (i) Flectol H is the chemical 1,2-Dihydro-2,2,4-trimethylquinoline, polymerized ($C_{12}H_{17}N$). It is a synthetic chemical not found in natural products, and has been used as a component of food packaging adhesives.

(ii) Food containing any added or detectable level of this substance is deemed adulterated in violation of the act based upon an order published in the FEDERAL REGISTER of April 7, 1967 (32 FR 5675).

(2) *4,4I -Methylenebis (2-choroanalineQ.* (i) 4,4'- Methylenebis (2-choroanaline) has the molecular formula, $C_{13}H_{12}Cl_2N_2$. It is a synthetic chemical not found in natural products and has been used as a polyurethane curing agent and as a component of food packaging adhesive and polyurethane resins.

(ii) Food containing any added or detectable level of this substance is deemed adulterated in violation of the act based upon an order published in the FEDERAL REGISTER of December 2, 1969 (34 FR 19073).

Interested persons may on or before October 24, 1973, file with the Hearing Clerk, Food and Drug Administration, Rm. 6–88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: July 19, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73–15216 Filed 7–25–73;8:46 am]

[21 CFR Part 121]

REMOVAL OF CERTAIN SUBSTANCES FROM THE GRAS LIST REVIEW

Notice of Withdrawal of Proposal

In the FEDERAL REGISTER of April 13, 1973 (38 FR 9310), the Commissioner of Food and Drugs proposed to delete 52 substances from the current GRAS review and to delist these same substances from § 121.101 (21 CFR 121.101). The basis for this proposed deletion and delisting was the absence of reported use or production of the substances during 1970. The use and production survey of the industry was conducted by the National Academy of Sciences, through its Food Protection Committee of the National Research Council, under contract with the Food and Drug Administration.

One hundred and eighty comments were received in response to the proposal. Eighty-seven of these comments indicated usage of the GRAS substances in animal feeds, 37 in nutrient pharmaceutical preparations, 18 in indirect food ingredients, and 38 in direct human food use.

In the direct human use category, the comments reported the use of 43 of the 52 GRAS substances listed in the proposal. These comments gave numerous reasons for not participating in the NAS Survey, including non-solicitation by NAS. Although most of the comments were in agreement with the intent of the proposal, each requested specific exceptions.

As a result of the above comments, the Commissioner recognizes that there is sufficient commercial interest in these GRAS food substances to retain them in the current GRAS review. Accordingly, notice is hereby given that the 52 substances as published in the FEDERAL REGISTER on April 13, 1973 (38 FR 9310), will remain in § 121.101 (21 CFR 121.101), pending the results of this review.

Dated: July 19, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73–15222 Filed 7–25–73;8:45 am]

[21 CFR Part 121]

CAROB BEAN GUM

Proposed Transfer From GRAS List to Food Additive Regulation for Direct Human Food Use and Affirmation of GRAS Status as Indirect Human Food Ingredient

The Food and Drug Administration is conducting a comprehensive study of direct human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. Pursuant to this review, the safety of carob bean gum has been evaluated. In accordance with the provisions of §§ 121.40 and 121.41, the Commissioner of Food and Drugs proposes to affirm the GRAS status of this ingredient for indirect human food use and to transfer the ingredient to a food additive regulation for direct human food use. The Commissioner also proposes to establish a new § 121.105, under which all indirect human food ingredients affirmed as GRAS will be listed.

As the review of GRAS and prior-sanctioned direct human food ingredients progresses, these ingredients will be

proposed for inclusion in new § 121.104 *Substances added directly to human food affirmed as generally recognized as safe (GRAS)*, proposed new § 121.106 *Substances prohibited from use in food*, Subpart D as direct human food additives, Subpart E as prior sanctions, or Subpart H as interim human food additives. Because § 121.101 is not limited to direct human food ingredients, and has been regarded also as the basis of GRAS determinations for indirect food ingredient sue, in or on food contact surfaces, and for use in pet food and animal feed, the Commissioner has concluded that when an ingredient listed in § 121.101 is affirmed for direct human food use it will be retained in § 121.101 with the explanation that it has been affirmed as GRAS and cross-referenced to the applicable paragraph in new § 121.104. Similarly, where it is affirmed as GRAS for indirect human food use and transferred to a food additive regulation for direct use, the same explanation will be provided, along with appropriate exceptions. This latter procedure is proposed with respect to carob bean gum.

Many of the substances published as GRAS § 121.101, or used on a determination that they are GRAS without publication in § 121.101, were approved by the United States Department of Agriculture for food packaging or processing use in meat or poultry, or were approved by the Food and Drug Administration for food packaging or processing pursuant to correspondence, regulations, informal announcements, or in other ways, prior to 1958. Thus, many of these ingredients are subject to specific prior sanctions for indirect human food use in addition to GRAS status. No comprehensive list of such prior sanctions exists. To the extent that one of these substances is affirmed as GRAS, the fact that it may also be subject to a prior sanction is largely of historical interest and has no regulatory significance. To the extent that one of these substances is not affirmed as GRAS, any restrictions or limitations imposed upon its use could in any event also be imposed on the prior-sanctioned uses under the adulteration provisions of the act as provided in § 121.-2000, published in the FEDERAL REGISTER of May 15, 1973 (38 FR 12738).

Accordingly, the Commissioner has concluded that regulations based upon the review of GRAS and prior-sanctioned indirect human food ingredients will initially be proposed on the assumption that no prior sanction exists. Because prior-sanctioned status constitutes an exemption from section 409 of the act, it should be construed narrowly, and the burden of coming forward with evidence of the sanction properly rests upon the person who asserts it. In the event that any person responds to a proposed regulation with proof of a valid prior sanction, a final regulation will be issued under Subpart E, "Substances for which prior sanctions have been granted," as well as under any other aplicable sections of the regulations. In this way, all possible uses of the ingredient will be fully covered. Any regulation promulgated pursuant to this review will constitute a determination that excluded uses would result in adulteration of the food in violation of section 402 of the act, and the failure to submit proof of an applicable prior sanction in response to any proposed regulation will also constitute a waiver of the right to asset such sanction at any later point in time. Any proposed regulation will also be construed as a proposal under Subpart E in the event that a prior sanction is asserted in comments submitted on it. This procedure is necessary because of the unavailability of any comprehensive list of prior sanctions.

Carob bean gum (locust bean gum) has been listed in § 121.101(d)(7), published in the FEDERAL REGISTER of November 20, 1959 (24 FR 9368), as GRAS as a stabilizer and in § 121.101(h) and (i) as GRAS for food contact surfaces. Carob bean, locust bean, and St. John's bread are also individually listed as GRAS in § 121.101(e)(2) as natural flavoring substances, as published in the FEDERAL REGISTER of January 19, 1960 (25 FR 404). These numerous listings, as well as the published literature, have caused a great deal of misunderstanding about the status of these substances. Carob bean gum, or its synonym locust bean gum, has been used in U.S. food production since 1925. It consists of the endosperm of the carob (locust) bean seed and usually the seed coat and germ. Carob bean, locust bean, and St. John's bread are all synonyms for the whole bean consisting of pod, pulp, and seed and can be compared to a whole string bean. The dried gum has been used as a stabilizer and thickener in foods and as a coating for food packaging containers. The whole bean is eaten as a green vegetable and also dried and ground for a multitude of human and animal food and food ingredient uses. This notice covers only the food ingredient uses of the gum, obtained from the carob (locust) bean seed, when used in human food. Food ingredient uses of the whole bean will be evaluated at a later date.

Carob bean gum (known also as locust bean gum) has been the subject of a search of the scientific literature from 1920 to the present. The parameters used in the search were chosen to discover any articles that considered (1) the chemical toxicity, (2) occupational hazards, (3) metabolism, (4) reaction products, (5) degradation products, (6) any reported caracinogenicity, teratogenicity or mutagenicity, (7) dose response, (8) reproductive effects, (9) histology, (10) embryology, (11) behavioral effects, (12) detection, and (13) processing. A total of 165 abstracts on carob (locust) bean gum were reviewed and 11 particularly pertinent reports from the literature survey have been summarized in a Scientific Literature Review.

A representative cross-section of food manufacturers was surveyed to determine the specific foods in which the carob bean gum was used and at what levels. Available surveys of consumer consumption were obtained and combined with the production information to obtain an estimate of the consumer exposure to carob bean gum. The total carob (locust) bean gum used in food in 1970 is reported to be about twice the amount used in 1960.

The Scientific Literature Review shows, among other studies, the following information as summarized in the report of the Select Committee on GRAS Substances:

Two Chick experiments are pertinent. In the first, 10 one-day-old Arbor Acres chicks were fed a stock diet; another comparable group was fed the stock diet plus a 2 percent cellulose supplement; and a third comparable group was fed a 2 percent carob bean gum supplement. The third group showed a 30 percent depressed feed intake after three weeks, with a corresponding decrease in weight as compared to the cellulose-fed group. Each chick consumed about 340 mg. of carob bean gum per day, or in excess of 2 g per kg per day. The degree of nitrogen retention and metabolizable energy content were about the same, as in the cellulose group, although the fat absorption was about 8 percent higher.

In the second test, similar groups of chicks were fed stock diets supplemented with 0.25, 0.5, 1.0, and 2.0 percent of carob bean gum. After three weeks, the chicks fed at the 2 percent level showed a 27 percent growth depression as compared to the controls, while those at the lower levels of supplement showed an average 6 percent growth depression. However, the authors provided no data on food intakes in this experiment. Others working with carob bean pods have shown that tannins depress appetite and growth. In addition, carob beans contain trypsin inhibitors which are known to have growth-inhibiting properties. Since tannins and trypsin inhibitors could be naturally present in the carob bean gum used in the chick studies, either or both could have accounted for the growth depression reported. From the data given, it is not possible to ascribe depression in growth to toxicity of the gum.

A 10 percent dietary supplement of carob bean gum does not significantly affect the growth of rats. Three groups of 8 rats averaging 44 g each were fed for 28 days on a stock diet, stock diet plus 1 percent cholesterol, and stock diet plus 1 percent cholesterol and 10 percent carob bean gum. Differences in weight gain among the three groups were not significant and no adverse effects were reported. While feed consumption was not reported, it is estimated that a 44-g rat would consume no less than 10 g per day of the 10 percent carob bean gum diet, which would be equivalent to 1 g of the gum per day. For a 44-g rat this intake rate would be about 23 g per kg per day.

Oral LD_{50} in the rat is reported to be greater than 5 g per kg for multiple doses, and greater than 10 g per kg for a single dose.

Clinical observations of 16 human infants showed no untoward effects from feeding a 1 percent carob bean gum powder, called "Nestargel," for an unstated period of time. The substance was apparently not changed by the saliva and gastric juice.

The fate of carob bean gum in the gastrointestinal tract of adults was followed by means of x-rays and stool examination. Eight adults were fed barium suspensions followed by "two heaping teaspoonfulls" of a gum preparation called "Vacuosa." The colloidal gel from the breakup of the "Vacuosa" peloids mixed thoroughly with the fecal masses in the colon. The carob bean gum did not disintegrate into the gelatinous state until it reached the large bowel. There was no evidence of interference with normal digestion. Actual body load of carob bean gum was not reported; but assuming 15 g per two tea-

spoonfuls, the gum must have been administered at a level of about 250 mg per kg.

Beyond these studies, there is no detailed information relating to the absorption, digestion, metabolism, or excretion of carob bean gum in man or animals.

Mutagenic tests on rats and mice using three different methods gave negative results. There was no measurable mutagenic response of alteration in the recombination frequency for *Saccharomyces cerevisiae* in either the host-mediated assay at levels as high as 5 g per kg or the associated in vitro tests. No adverse effects were observed on either metaphase chromosomes from rat bone marrow or anaphase chromosomes from in vitro cultures of human lung cells at any of the doses or time periods tried. No significant adverse responses were noted in the dominant lethal gene test on rats.

Teratologic tests on four species of animals were negative. Ora intubation of up to 1.3 g per kg of body weight of carob beans gum in anhydrous corn oil to pregnant rats for 10 consecutive days, or up to 1.0 g per kg to pregnant hamsters for 5 consecutive days, produced no clearly discernible effect on nidation or on materna or feta surviva. The frequency of abnormalities in either soft or skeletal tissues of the test animals was comparabe to that occurring spontaneousy in the sham-treated controls. In mice, no untoward teragogenic or maternal effects were noted at a level of 280 mg per kg for 10 consecutive days. At 1.3 g per kg, 5 out of 21 dams died. The surviving dams produced normal litters. In pregnant rabbits, no untoward effects were noted at a level of 196 mg per kg for 13 consecutive days, but at 910 mg per kg, a majority of the dams died. The surviving dams produced normal litters.

No evidence of carcinogenic or allergenic activity of carob bean gum has been found in the literature surveyed.

All of the available safety information on carob bean gum has been carefully evaluated by qualified scientists of the Select Committee on GRAS Substances selected by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology (FASEB). It is the opinion of the Select Committee that: "The available information contains no evidence demonstrating that carob bean gum constitutes a hazard to the public when used in the manner and quantity now practiced. However, it is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard."

Based upon his own evaluation of all available information, the Commissioner concurs with this conclusion. In addition the Commissioner concludes that continued safe use of carob (locust) bean gum will require food additive regulation of the ingredient to preserve present levels of use. The levels of use adopted in this proposal, for various categories of food, are those reported to the National Academy of Sciences in their Survey of food manufacturers. The Commissioner further concludes that indirect human food use of carob (locust) bean gum, as a food contact surface in packaging, does not contribute significantly to the carob bean gum content of the packaged food and should thus be affirmed as GRAS for this purpose.

Neither of these proposed actions affects the present use of carob (locust) bean gum for pet food or animal feed or the present uses of carob bean meal and powder, when made from the whole carob bean pod with seed, or carob bean as a raw agricultural commodity.

Copies of the Scientific Literature Review on carob bean gum and the report of the FASEB Committee are available for review at the office of the Hearing Clerk, Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20852, and may be purchased from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22151.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409(d), 701(a), 52 Stat. 1055, 72 Stat. 1784, 1787; 21 U.S.C. 321(s), 348(d), 371(a)), and under authority delegated to him (21 CFR 2.120), the Commissioner proposes that Part 121 be amended as follows:

1. By amending § 121.101(d)(7) to add the explanation "food additive regulation § 121.1251; affirmed as GRAS § 121.105(f)(1)" after "Carob bean gum (locust beam gum)" to read as follows:

§ 121.101 Substances that are generally recognized as safe.

* * * * * *

(d) * * *

Product	Tolerance	Limitations, restrictions or explanations
* * *	* * *	* * *
(7) STABILIZERS		
* * *	* * *	* * *
Carob bean gum (locust bean gum).		Food additive regulation § 121.1251; affirmed as GRAS § 121.105(f)(1).
* * *	* * *	* * *

2. By adding to Subpart B a new section, as follows:

§ 121.105 Substances in food contact surfaces affirmed as generally recognized as safe (GRAS).

(a) The indirect human food ingredients listed in this section have been reviewed by the Food and Drug Administration and determined to be generally recognizd as safe (GRAS) for the purposes and under the conditions prescribed.

(b) This section does not authorize direct addition of any food ingredient to a food. It authorizes only the use of these ingredients as indirect ingredients of food, through migration from their immediate wrapper, container, or other food contact surface. Any migration or use levels included in this section represent maximum levels under current good manufacturing practice.

(c) The listing of a food ingredient in this section does not authorize the use of such substance for the purpose of adding the ingredients to the food through extraction from the food contact surface.

(d) The listing of a food ingredient in this section does not authorize the use of such substance in a manner that may lead to deception of the consumer or to any other violation of the act.

(e) If the Commissioner of Food and Drugs is aware of any prior sanction for use of an ingredient under conditions different from those proposed to be affirmed as GRAS, he will concurrently propose a separate regulation covering such use of the ingredient under Subpart E of this part. If the Commissioner is unaware of any such applicable prior sanction, the proposed regulation will so state and will require any person who intends to assert or rely on such sanction to submit proof of its existence. Any regulation promulgated pursuant to this section constitutes a determination that excluded uses would result in adulteration of the food in violation of section 402 of the act, and the failure of any person to come forward with proof of such an applicable prior sanction in response to the proposal will constitute a waiver of the right to assert or rely on such sanction at any later time. The notice will also constitute a proposal to establish a regulation under Subpart E, incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable prior sanction in response to the proposal.

(f) The following indirect human food ingredients have been affirmed as GRAS:

(1) *Carob (locust) bean gum.* (i) Carob bean gum (also called locust bean gum) is the material obtained from the ground endosperm of the seed of the *Ceratonia siliqua* (Linne), a leguminous evergreen tree.

(ii) The ingredient meets specifications of the Food Chemicals Codex 2nd Ed. (1972).[1]

(iii) The ingredient is used or intended for use as a constituent of food packaging containers and thus may only become a component of food through migration from this surface.

(iv) The ingredient migrates to the packaged or wrapped food at levels not to exceed good manufacturing practices.

3. By adding to Subpart D a new section as follows:

121.1251 Carob bean gum (locust bean gum).

The food additive carob bean gum may be safely used in food in accordance with the following conditions:

(a) Carob bean gum (locust bean gum) is the material obtained from the ground endosperm of the seed of the *Ceratonia siliqua* (Linne), a leguminous evergreen tree.

(b) The additive meets specifications of the Food Chemicals Codex 2nd Ed. (1972).[1]

(c) The additive is used at not to exceed the following maximum levels:

[1] Copies may be obtained from: National Academy of Sciences 2101 Constitution Ave., N.W. Washington, D.C. 20037.

MAXIMUM USAGE LEVELS

Food	Permitted Percent	Function
Baked goods and baking mixes, § 121.1(l)(1)	0.15	Flavoring agent, § 121.1(m)(11); stabilizer and thickener, § 121.1(m)(26).
Beverages and beverage bases, nonalcoholic, § 121.1(l)(3).	0.25	Flavoring agent, § 121.1(m)(11); stabilizer and thickener, § 121.1(m)(26).
Cheeses, § 121.1(l)(5)	0.75	Stabilizer and thickener, § 121.1(m)(26).
Gelatins, puddings, and fillings, § 121.1(l)(22)	0.40	Stabilizer and thickener, § 121.1(m)(26).
All other food categories	0.50	Flavoring agent, § 121.1(m)(11); stabilizer and thickener, § 121.1(m)(26).

(d) The label and labeling of the additive and any intermediate mix of the additive for use in finished food shall bear, in addition to the other labeling required by the act:

(1) The name of the additive;

(2) A statement of the concentration of the additive in any intermediate mix; and

(3) Adequate information to assure that the final food product complies with the limitations prescribed in paragraph (c) of this section.

The Commissioner hereby gives notice that he is unaware of any prior sanction for the use of this ingredient in food under conditions different from those proposed above. Any person who intends to assert or rely on such a sanction shall submit proof of its existence in response to this proposal. The regulation proposed above will constitute a determination that excluded uses would result in adulteration of the food in violation of section 402 of the act, and the failure of any person to come forward with proof of such an applicable prior sanction in response to this proposal constitutes a waiver of the right to assert or rely on such sanction at any later time. This notice also constitutes a proposal to establish a regulation under Subpart E, incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable prior sanction in response to this proposal.

Interested persons may, on or before October 24, 1973, file with the Hearing Clerk, Food and Drug Administration, Rm. 6–88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: July 19, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73–15215 Filed 7–25–73;8:45 am]

[21 CFR Part 121]

FOOD CATEGORIES AND FOOD INGREDIENT FUNCTIONS

Proposed Designation

The Food and Drug Administration is conducting a study of the direct human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. As this study progresses, the Commissioner of Food and Drugs will publish in the FEDERAL REGISTER, appropriate proposals to (1) affirm GRAS status, (2) publish a prior sanction, (3) establish an interim food additive regulation, (4) establish a permanent food additive regulation, or (5) eliminate food use of the ingredient under review. The Commissioner is proposing regulations in this issue of the FEDERAL REGISTER with respect to the first ingredients subject to this review.

In regulations published since 1958 under the Food Additives Amendment, it has frequently been appropriate to designate broad food categories in which an ingredient may properly be used, and to state the functional purpose for which the ingredient may be used. To date, no standardized definitions of the food categories or functional descriptions have been adopted.

In conducting the industry survey of production and use of GRAS and prior-sanctioned food substances, under contract with the Food and Drug Administration, for use in the review of the safety of these ingredients, the National Academy of Sciences developed standardized food categories. Food categories of a similar type were also used by the United States Department of Agriculture and the Market Research Corporation of America (MRCA), in their respective surveys, to determine the sizes of servings used by consumers and the frequency of consumption of specific foods.

The Commissioner has concluded that the food categories adopted by the National Academy of Sciences (NAS) represent a valid and useful method of dividing food products into general classes of related products. Where tolerances or limitations are established for the use of direct human food ingredients, and there is significant variation with respect to appropriate tolerances or limitations for one or more specific food categories, this method of classification will permit designation of the foods to be covered without requiring a detailed list of each of the individual products included. In many instances, tolerances or limitations may be imposed uniformly for all foods. It may also be necessary to impose, with relatively few exceptions, tolerances or limitations for specific food categories at levels higher or lower than the general rule. It is the Commissioner's intent to utilize the broadest possible approach, in the interests of simplification, wherever justified by the available safety data and information.

It is appropriate that the same food classification system developed by the NAS for its production and consumption survey should also be utilized by the Food and Drug Administration in imposing tolerances and limitations for use of specific ingredients. NAS Survey data was accumulated using these food categories, and they are consequently of great assistance in determining whatever tolerances and limitations are justified. The same classification system, already cross-indexed to the MRCA and USDA consumption data, also provides an immediate reference to consumption patterns on which those tolerances and limitations are in part based.

The proposal set out below contains a general description of each food category, without attempting to list in detail all the products within it. Wherever any question arises with respect to the proper classification of a specific food product which might reasonably fall within two or more categories, proper classification will be determined by referring to the more detailed and specific classification lists established by the MRCA and cross-indexed to NAS food categories, as contained in the final NAS report to the Food and Drug Administration. The Final Report of the NAS is now available from the National Technical Information Service (NTIS), in accordance with the notice on this matter published in this issue of the FEDERAL REGISTER. Accordingly, the Commissioner is incorporating this specific classification list, by reference, into this proposed regulation, for purposes of resolving close questions with respect to proper classification.

The NAS also found it necessary to establish a similar classification system with respect to the technical functions performed by the various specific ingredients directly added to human food. These functional effects are contained in the final NAS report to the Food and Drug Administration and are the subject of production, use, and consumption data on the technical functions of numerous food ingredients, added to the various NAS food categories. Thus, these tables describe the specific technical purposes for which GRAS and prior-sanctioned ingredients are added to NAS food categories, and they consequently serve as an excellent reference to consumption patterns on which ingredient tolerances and limitations are in part based. Accordingly, the Commissioner is proposing to standardize the technical functional descriptions submitted by the NAS, so that regulations permitting the use of ingredients in food will accurately describe their purpose. A standardized system of classification will also assist consumers in understanding the functions performed by these ingredients in the foods they consume.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784–1788 as amended; 21 U.S.C. 321(s), 348, 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes to amend Part 121 by adding to § 121.1 the following two new paragraphs:

§ 121.1 Definitions and interpretations.

* * * * *

(l) The following general food categories are established to group specific related foods together for the purpose of establishing tolerances or limitations for the use of direct human food ingredients. Individual food products will be classified within these categories according to the detailed classification lists contained in Exhibit 33B of the report of the National Academy of Sciences on "A Comprehensive Survey of Industry on the use of Food Chemicals Generally Recognized as Safe" (September 1972).[1]

(1) Baked goods and baking mixes (includes ready-to-eat or ready-to-bake products and all dry flour, meal, and multipurpose mixes).

(2) Beverages, alcoholic (includes malt beverages, wines, and distilled liquors).

(3) Beverages and beverage bases, non-alcoholic (includes dry and liquid imitation concentrates and ready-to-drink products, except for coffee or tea).

(4) Breakfast cereals (includes cold and hot breakfast cereals).

(5) Cheeses (includes standardized, non-standardized, snack, and other miscellaneous cheeses).

(6) Chewing gum (includes all flavored gums).

(7) Coffee and tea (includes regular and instant products).

(8) Condiments and relishes (includes plain seasoning sauces and spreads, olives, pickles, and relishes).

(9) Confections and frostings (includes candy and flavored frostings and frosting sugars).

(10) Dairy product analogs (includes non-dairy derived products such as toppings, toppings, mixes, and coffee whiteners.

(11) Egg products (includes liquid, frozen, or dried eggs, and egg products).

(12) Fats and oils (includes salad dressings, margarines, butter, and cooking oils).

(13) Fish products (includes all prepared or frozen products containing fish, shellfish, and other aquatic animals, except fresh fish).

(14) Fresh eggs (includes only whole fresh eggs).

(15) Fresh fish (includes only fresh and home-frozen fish, shellfish, and other aquatic animals).

(16) Fresh fruits and fruit juices (includes only raw fruits and fruit juices and fruit blends).

(17) Fresh meats (includes only fresh and home-frozen beef, pork, lamb, and game animals).

(18) Fresh poultry (includes only fresh and home-frozen poultry).

(19) Fresh vegetables and potatoes (includes only fresh, home-canned, and home-frozen vegetables and potatoes).

(20) Frozen dairy desserts and mixes (includes ice cream, ice milk, sherbets, and frozen novelties).

(21) Fruit and water ices (includes all frozen fruit and water ices).

(22) Gelatins, puddings, and fillings (includes flavored gelatins, puddings, custards, parfaits, and pie fillings).

(23) Grain products and pastas (includes macaroni, noodle, and rice dishes, without meat or vegetables).

(24) Gravies and Sauces (includes flavored meat souces, gravies, and marinades).

(25) Hard candy and cough drops (includes all hard sucker type candies).

(26) Herbs, seeds, spices, seasonings, blends, extracts, and flavorings (includes all natural spices and blends and artificial flavors).

(27) Jams and jellies, homemade (includes fruit butters and preserves).

(28) Jams, jellies, and sweet spreads (includes fruit butters and preserves).

(29) Meat products (includes all prepared and frozen products containing beef, pork, or lamb).

(30) Milk, whole and skim (includes only whole and skim milks).

(31) Milk products (includes dried and fluid milk products such as concentrated, evaporated, and flavored milk, and cream products).

(32) Nuts and nut products (includes whole or shelled nuts, coconut, and nut spreads).

(33) Poultry products (includes all prepared and frozen products containing poultry).

(34) Processed fruits and juices (includes canned or frozen fruits and fruit juices, concentrates, dilutions, ades, and drink substitutes).

(35) Processed vegetables and juices (includes canned or frozen vegetables, vegetable juices, and blends).

(36) Reconstituted vegetable proteins (includes only meat substitute products and dishes).

(37) Snack foods (includes chips, pretzels, and other novelty snacks).

(38) Soft candy (includes all soft and nougat candies).

(39) Soups, homemade (includes all homemade soups).

(40) Soups and soup mixes (includes all meat and vegetable soups).

(41) Sugar, white, granulated (includes only white granulated sugar).

(42) Sugar substitutes (includes all forms of sugar substitutes).

(43) Sweet sauces, toppings, and syrups (includes all fruit, berry, or other flavored products).

(m) The following terms describe the physical or technical functional effects for which direct human food ingredients may be added to foods. They are adopted from the National Academy of Sciences national survey of food industries, reported to the Food and Drug Administration under the contract title, "A Comprehensive Survey of Industry on the Use of Food Chemicals Generally Recognized as Safe" (September 1972).

(1) "Anticaking agents and free-flow agents": substances added to finely powdered or crystalline food products to prevent caking, lumping, or agglomeration.

(2) "Antioxidants": substances used to retard deterioration, rancidity, or discoloration due to oxidation.

(3) "Colors and coloring adjuncts" (including color stabilizers, color fixatives, color-retention agents, etc.): substances used to impart, preserve, or enhance the color or shading of a food.

(4) "Curing and pickling agents": substances imparting a unique flavor and/or color to a foodstuff, usually producing an increase in shelf life stability.

(5) "Dough conditioners" (including yeast foods): substances used to modify the gluten and enhance the property of making an elastic and stable dough.

(6) "Drying agents": substances with moisture-absorbing ability, used to maintain an atmosphere of low moisture.

(7) "Emulsifiers and emulsifier salts": substances which modify surface tension in the component phase of an emulsion to establish a uniform dispersion or emulsion.

(8) "Enzymes": enzymes used to improve food processing.

(9) "Firming agents": substances added to precipitate residual pectin, thus strengthening the supporting tissue and preventing its collapse during processing.

(10) "Flavor enhancers": substances added to supplement, enhance, or modify the original taste and/or aroma of a food without imparting a characteristic taste or aroma of its own.

(11) "Flavoring agents and adjuvants": substances added to impart or help impart a taste or aroma.

(12) "Flour-treating agents" (including bleaching and maturing agents): substances added to milled flour to improve its color and baking qualities.

(13) "Formulation aids" (including carriers, binders, fillers, plasticizers, film-formers, and tableting aids, etc): substances used to promote or produce a physical state or texture in food.

(14) "Fumigants": volatile substances used for controlling insects or pests.

(15) "Humectants" (including moisture-retention agents and anti-dusting agents): hygroscopic substances incorporated in food to promote retention of moisture.

(16) "Leavening agents": substances used to produce carbon dioxide in baked goods to impart a light texture.

(17) "Lubricants and release agents": substances added to food contact surfaces to prevent confections and baked goods from sticking to their containers.

(18) "Non-nutritive sweetners": substances used as a substitute for sugar when intake of sugar or its bulk is undesirable.

(19) "Nutrient supplements": food components, or their synthetic substitutes, which are necessary for the body's nutritional and metabolic processes.

(20) "pH control agents" (including buffers, acids, alkalies, and neutralizing agents): substances added to change or maintain active acidity or basicity.

(21) "Preservatives" (including antimicrobial agents, fungistats, and mold and rope inhibitors, etc.): substances added to prevent growth of contaminating microorganisms and subsequent spoilage.

(22) "Processing aids" (including clarifying agents, clouding agents, cata-

[1] Copies may be obtained from: National Technical Information Service (NTIS) 5285 Port Royal Road Springfield, VA 22151

lysts, flocculents, and filter aids, etc.): substances used as manufacturing aids to enhance the appeal or utility of a food or food component.

(23) "Propellants, aerating agents, and gasses": chemically inert gasses used to supply force to expel a product or used to reduce the amount of oxygen in contact with the food in packaging processes.

(24) "Sequestrants": substances which combine with polyvalent metal ions to form a soluble metal complex, to improve the quality and stability of products.

(25) "Solvents and vehicles": substances used to extract or dissolve another substance.

(26) "Stabilizers and thickeners" (including suspending and bodying agents, setting agents, jelling agents, and bulking agents, etc.): substances used to produce viscous solutions or dispersions, to impart body, improve consistency, or stabilize emulsification.

(27) "Surface—active agents" (other than emulsifiers, but including solubilizing agents, dispersants, detergents, wetting agents, rehydration enhancers, whipping agents, foaming agents, and defoaming agents, etc.): substances used to modify surface properties of food components for a variety of effects.

(28) "Surface—finishing agents" (including glazes, polishes, waxes, and protective coatings): substances used to increase palatability, preserve gloss, and inhibit discoloration of foods.

(29) "Sweeteners": substances used to sweeten the taste of food.

(30) "Synergists": substances used to act or react with another food ingredient to produce a total effect different or greater than the sum of the individual effects.

(31) "Texturizers": substances which affect the appearance or feel of the composition of a food.

Interested persons may, on or before October 24, 1973, file with the Hearing Clerk, Food and Drug Administration, Room 6–88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: July 19, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73–15217 Filed 7–25–73;8:45 am]

[21 CFR Part 121]

MANNITOL AND SORBITOL

Affirmation of GRAS Status of Direct Human Food Ingredients

The Food and Drug Administration is conducting a comprehensive study of direct human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. Pursuant to this review, the safety of mannitol and sorbitol has been evaluated. In accordance with the provisions of § 121.40, the Commissioner of Food and Drugs proposes to affirm the GRAS status of these two ingredients.

Mannitol (1,2,3,4,5,6-hexanehexol) and its sterioisomer sorbitol are both solid hexahydric alcohols prepared commercially by catalytic reduction of glucose. Both occur naturally in small amounts in a variety of foods. Mannitol is found in olives, beets, celery and in the exudate of certain trees. Sorbitol is a normal constituent of such fruits as cherries, plums, pears, apples, and many berries.

Mannitol and sorbitol were listed in § 121.101(d)(2) as GRAS for use in special dietary foods at a maximum of 5 percent and 7 percent respectively in the FEDERAL REGISTER of January 31, 1961 (26 FR 938). Subsequently, food additive regulations were published for mannitol under § 121.1115 in the FEDERAL REGISTER of August 9, 1961 (28 FR 1540) and for sorbitol under § 121.1053 in the FEDERAL REGISTER of February 19, 1963 (26 FR 7127) to provide for other uses of these substances, with levels for use being restricted only to the amount reasonably required to accomplish the intended effect.

Mannitol and Sorbitol have been the subject of a search of the published scientific literature from 1920 to the present. The parameters used in the search were chosen to discover any articles that considered (1) chemical toxicity, (2) occupational hazards, (3) metabolism, (4) reaction products, (5) degradation products, (6) reported carcinogenicity, teratogenicity, or mutagenicity, (7) dose sponse, (8) reproductive effects, (9) histology, (10) embryology, (11) behavioral effects, (12) detection methodology and (13) processing. A total of 968 abstracts on mannitol were reviewed and 11 particularly pertinent reports from the literature survey have been summarized in a Scientific Literature Review. A total of 870 abstracts on sorbitol were reviewed and 26 particularly pertinent reports from the literature survey have been summarized in a Scientific Literature Review.

A representative cross-section of food manufacturers was surveyed to determine the specific foods in which these substances were used and at what levels. Available surveys of consumer consumption were obtained and combined with the production information to obtain an estimate of the consumer exposure to mannitol and sorbitol. The total mannitol used in food in 1970 is reported to be about 90 times that used in 1960. The total sorbitol used in food in 1970 is reported to be about seven times that used in food in 1960.

The Scientific Literature Review shows, among other studies, the following information as summarized in the report of the Select Committee on GRAS Substances:

Mannitol is absorbed from the gastrointestinal tract of animals and man, and does not accumulate in the organism; it is partially metabolized and partly excreted in the urine. There is evidence that the intestinal flora may convert mannitol to more readily utilized substances and this transformation may influence the reported amount of mannitol absorbed and metabolized by the liver. A wide variety of microorganisms and fungi convert mannitol to sugars and other carbohydrate fragments.

The absorption of mannitol in a 50 cm segment of the proximal small intestine, in children varying in age from 8 months to 4 years, has been reported. The mannitol was perfused in an isotonic solution in concentrations varying from 50 to 150 millimoles per liter. From 9 to 18 percent of the mannitol was found to be absorbed.

A more extensive study in 16 human adult volunteers, ranging in age from 20 to 66, revealed that, in the oral dosage range of 40 to 100 g, 65 percent of the ingested mannitol was absorbed. Of the absorbed mannitol, about a third was excreted intact in the urine and the remainder was oxidized to carbon dioxide. Excretion was virtually complete by four days, with about 91 percent excreted within the first day.

In experiments where 25 g of mannitol were fed to normal men, little evidence was found that the substance was utilized, as measured by blood sugar levels or respiratory quotients. The threshold laxative dose was found to be between 10 and 20 g of mannitol as compared with 50 g of sorbitol.

There are no reported long-term animal feeding studies (extending for more than half of the life span of the species) on mannitol. Relevant short-term animal studies and studies on man are summarized below.

The oral LD_{50} for the mouse is reported to be 22 g per kg, and for the rat to be 17.3 g per kg. The minimum lethal dose for the rat is reported to be greater than 13 g per kg.

In rats and monkeys fed mannitol (5 percent of the rat diet, and 3 g daily to monkeys) no significant chronic toxicity was observed over a period of 3 months. A study on one man, fed 10 g daily for a month, revealed no evidence of toxicity; but the same authors have shown that the ingestion of 10 to 20 g of crystalline mannitol as part of the diet results in a laxative effect. The latter observation has been confirmed.

Preliminary teratologic tests in mice, rats, and hamsters have been negative. Oral doses up to 1.6 g per kg of body weight of mannitol to pregnant mice and rats for 10 consecutive days, or up to 1.2 g per kg of body weight to pregnant hamsters for 5 consecutive days, produced no clearly discernible effects or nidation or on maternal or fetal survival. The frequency of abnormalities in either soft or skeletal tissues of the test animals was comparable to that occurring spontaneously in the sham-treated controls.

The Select Committee is unaware of any reports on mannitol indicating evidence of its carcinogenicity, mutagenicity, or effects on reproduction.

When injected intravenously, mannitol is filtered by the glomeruli of the kidneys and not appreciably reabsorbed by the tubles. For this reason, mannitol has been employed extensively as a substance to measure glomerular filtration rate in man. It has also been used medically as an intravenous diuretic, to lower intracranial pressure, and to decrease intraocular pressure in glaucoma. This wide usage of mannitol has not resulted in untoward toxic effects. However, a single allergic reaction to mannitol was observed when the substance was administered intravenously for the treatment of glaucoma. In the experience of these investigators, over 1500 patients had received similar medication without a serious allergic reaction. It appears from this report that allergic reactions to mannitol are possible, but that it does not constitute a dietary hazard for this reason.

The Joint FAO/WHO Expert Committee on Food Additives classified mannitol, in amounts of 50–150 mg per kg of body weight daily, as "conditionally acceptable". This term means that the substance may be employed within the specified limits with an

adequate margin of safety if it has been reviewed by experts for a particular use.

Orally administered sorbitol is absorbed and metabolized rapidly by man through normal glycolytic pathways, ultimately to carbon dioxide and water. After a 35 g dose (equivalent to 583 mg per kg) in normal and in diabetic adults, for example, less than 3 percent of the sorbitol was excreted in the urine in any case and the concentration of sorbitol in the blood was found to be immeasurably small. No evidence of toxicity was reported.

The oral LD_{50} of sorbitol in male and female mice is reported to be 23,200 and 25,700 mg per kg respectively; in male and female rats, 17,500 and 15,900 mg per kg respectively. The oral LD_{100} for the male rate is separately reported as 26,000 mg per kg.

The following short term studies of the oral administration of sorbitol are relevant:

In 40 g male rats, fed 5 percent sorbitol in a balanced diet, no toxic effects were observed during the three months of feeding. Feed consumption is not reported, but estimates based on other data presented indicate that sorbitol was being fed at a level of approximately 5 g per kg per day.

Rhesus monkeys fed sorbitol at a level of 8 g per kg per day for 3 months remained unaffected.

Man, consuming 10 g of sorbitol each day (equivalent to 167 mg per kg) for one month remained unaffected.

Normal children, 5–6 years old and normal infants, 20–35 months old, fed 9.3 g of sorbitol (equivalent to 500 or more mg per kg) remained unaffected except for the appearance of diarrheal stools in the younger group.

The laxative threshold for sorbitol, established in 12 normal adults, has been reported to be 50 g (equivalent to 833 mg per kg). It is also reported, in a study involving 86 volunteers, that a dosage level of 25 g per day in two doses does not cause laxation.

The following long-term studies of the oral administration of sorbitol are relevant:

Rats fed 5 percent sorbitol (equivalent to 5 g per kg per day) through three generations showed no deleterious effects on growth rate or liver glycogen storage capacity. There were no gross or histological abnormalties in kidney, liver, spleen, pancreas, or duodenum attributable to sorbitol. A subsequent report has indicated that weanling rats, given sorbitol at levels of 10 to 15 percent in the diet for 17 months and observed over 4 successive generations, showed no evidence of deleterious effects on weight gain, reproduction, lactation, or histological appearance of the main organs.

Rats fed 16 percent sorbitol for 19 months showed a tendency to become hypercalcemic after one year, with the appearance in some animals of bladder concretions and a generalized thickening of the skeleton. No feed consumption or animal weight figures were reported, but sorbitol level was estimated to be of the order of 16 g per kg.

No oral studies of the carcinogenic activity of sorbitol have been reported. However, studies in rats revealed that injected sorbitol, in the form of an iron-sorbitol citric acid product (Jectofer), produced no injection site tumors.

Sorbitol, at dose levels of 5 g per kg did not produce any measurable mutagenic response in the host-mediated assay in mice, in the metaphase chromosomes of rat bone marrow, or in the dominant lethal test in the rat. A slight increase was noted in the mitotic recombination frequency for *Saccharomyces cerevisiae* in the host-mediated assay, and a moderate, dose-related adverse effect was exhibited by human embryonic lung cells scored at anaphase.

Sorbitol elicited no teratogenic response in pregnant mice or rats fed a daily dose of 1600 mg per kg for 10 days, or in hamsters fed 1200 mg per kg per day for 5 days.

The Joint Food and Agriculture Organization/World Health Organization Committee on Food Additives indicates the acceptable daily intake of sorbitol for man as follows: "Conditional acceptance (as a food additive or as a food) not limited".

All of the available safety information has been carefully evaluated by qualified scientists of the Select Committee on GRAS Substances selected by the Life Sciences Office of the Federation of American Societies for Experimental Biology (FASEB). It is the opinion of the Select Committee that there is no evidence in the available information on sorbitol and mannitol that demonstrates a hazard to the public when they are used at current levels or at levels that may reasonably be expected in the future. Based upon his own evaluation of this information the Commissioner concurs with this conclusion.

Copies of the Scientific Literature Reviews on mannitol and sorbitol and the reports of the FASEB Committee are available for review at the office of the Hearing Clerk, Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20852, and may be purchased from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22151.

Therefore, pursuant to provisions of the Federal Food, Drug and Cosmetic Act (secs. 201(s), 409(d), 701(a), 52 Stat. 1055, 72 Stat. 1784, 1787; 21 U.S.C. 321(s), 348(d), 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes that Part 121 be amended as follows:

1. In the table in § 121.101(d) by amending the listing for "Mannitol" and "Sorbitol" in the "Tolerance" and in the "Limitations, restrictions or explanations" columns in subparagraph (d)(5) to read as follows:

§ 121.101 Substances that are generally recognized as safe.

* * * * *

(d) * * *

Product	Tolerance	Limitations, restrictions or explanations
* * *	* * *	* * *
(5) NUTRIENTS AND/OR DIETARY SUPPLEMENTS[1]		
* * *	* * *	* * *
Mannitol		Affirmed as GRAS § 121.104(g)(3).
* * *	* * *	* * *
Sorbitol		Affirmed as GRAS § 121.104(g)(4).
* * *	* * *	* * *

§§ 121.1053 and 121.1115 [Revoked].

2. By revoking § 121.1053 and § 121.1115

3. By amending proposed new § 121.104 to add the following two new subparagraphs to paragraph (g).

§ 121.104 Substances added directly to human food affirmed as generally recognized as safe (GRAS).

* * * * *

(g) * * *

(3) *Mannitol.* (i) Mannitol is the chemical 1,2,3,4,5,6,-hexanehexol ($C_6H_{14}O_6$), produced by the electrolytic reduction of glucose, differing principally from sorbitol by having a different optical rotation.

(ii) The ingredient meets the specifications of the Food Chemicals Codex 2nd Ed. (1972)[1].

(iii) The ingredient is used as a sweetener, formulating aid, stabilizer and thickener, and surface-finishing agent.

(iv) The ingredient is used in food at levels not to exceed good manufacturing practices. The 1972 NAS–NRC Survey indicates current good manufacturing practice in the use of mannitol results in a maximum of 33 percent in hard candy (§ 121.1(l) (25)3, 25 percent in chewing gum] 121.1(l) (6), 40 percent in soft candy (§ 121.1(l) (38)), 8 percent in confections and frostings (§ 121.1(l) (9)), and at less than 2.5 percent in all other foods.

(v) The label and labeling of food whose reasonably foreseeable consumption may result in a daily ingestion of 20 grams of mannitol shall bear the statement: "Excess consumption may have a laxative effect."

(4) *Sorbitol.* (i) Sorbitol is the chemical 1,2,3,4,5,6,-hexanehexol ($C_6H_{14}O_6$), produced by the electrolytic reduction of glucose, differing principally from mannitol by having a different optical rotation.

(ii) The ingredient meets the specifications of the Food Chemicals Codex 2nd Ed. (1972)[1].

(iii) The ingredient is used as a sweetener, formulating aid, emulsifier, humectant, stabilizer and thickener, texturizer, lubricant, and anticaking agent.

(iv) The ingredient is used in foods at levels not to exceed good manufacturing practices. The 1972 NAS—NRC Survey indicates current good manufacturing practice in the use of sorbitol results in a maximum of 97 percent in hard candy (§ 121.1(l)(25)), 62 percent in chewing gum (§ 121.1(l)(6)), 98 percent in soft candy (§ 121.1(l)(38)), 17 percent in frozen dairy desserts and mixes (§ 121.1(l)(20)), 30 percent in baked goods and baking mixes (§ 121.1(l)(1)), and 8 percent or less in all other foods.

(v) The label and labeling of food whose reasonably forseeable consumption may result in a daily ingestion of 50 grams of sorbitol shall bear the statement: "Excess consumption may have a laxative effect."

[1] Copies may be obtained from: National Academy of Sciences, 2101 Constitution Avenue, N.W. Washington, D.C. 20037.

The Commissioner hereby gives notice that he is unaware of any prior-sanction for the use of this ingredient in food under the conditions different from those proposed above. Any person who intends to assert or rely on such a sanction shall submit proof of its existence in response to this proposal. The regulations proposed above will constitute a determination that excluded uses would result in adulteration of the food in violation of section 402 of the act, and the failure of any person to come forward with proof of such an applicable prior-sanction in response to this proposal constitutes a waiver of the right to assert or rely on such sanction at any later time.

This notice also constitutes a proposal to establish a regulation under Subpart E, incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable prior-sanction in response to this proposal.

Interested persons may, on or before October 24, 1973, file with the Hearing Clerk, Food and Drug Administration, Rm. 6–88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: July 19, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73–15214 Filed 7–25–73;8:45 am]

[21 CFR Part 121]

METHYL PARABEN AND PROPYL PARABEN

Affirmation of GRAS Status of Direct Human Food Ingredients

The Food and Drug Administration is conducting a comprehensive study of direct human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. Pursuant to this review, the safety of methyl paraben and propyl paraben has been evaluated. In accordance with the provisions of § 121.40, the Commissioner of Food and Drugs proposes to affirm the GRAS status of these two ingredients. The Commissioner also proposes to establish a new § 121.104, under which all direct human food ingredients affirmed as GRAS will be listed.

As the review of GRAS and prior-sanctioned direct human fool ingredients progresses, these ingredients will be proposed for inclusion in new § 121.104 *Substances added directly to human food affirmed as generally recognized as safe (GRAS)*, proposed new § 121.106 *Substances prohibited from use in food*, Subpart D as direct human food additives, Subpart E as prior sanctions, or Subpart H as interim food additives. Because § 121.101 is not limited to direct human food ingredients, and has been regarded also as the basis of GRAS determinations for indirect food ingredient use (in or on food contact surfaces), and for use in pet food and animal feed, the Commissioner has concluded that when an ingredient listed in § 121.101 is affirmed for direct human food use, it will be retained in § 121.101 with the explanation that it has been affirmed as GRAS and cross-referenced to the applicable paragraph in new § 121.104. This procedure is proposed with respect to methyl paraben and propyl paraben.

Many of the substances published as GRAS in § 121.101, or used on a determination that they are GRAS without publication in § 121.101 were approved by the United States Department of Agriculture for use in meat or poultry, or were approved by the Food and Drug Administration for use in various foods pursuant to correspondence, food standards, regulations, informal announcements, or in other ways, prior to 1958. Thus, many of these ingredients are subject to specific prior sanctions in addition to GRAS status. No comprehensive list of such prior sanctions exists. To the extent that one of these substances is affirmed as GRAS for all prior-sanctioned uses, the fact that it may also be subject to a prior sanction is largely of historical interest and has no regulatory significance. To the extent that one of these substances is not affirmed as GRAS for all prior-sanctioned uses, any restrictions or limitations imposed upon its use could in any event also be imposed on the prior-sanctioned uses under the adulteration provisions of the act as provided in § 121.2000, published in the FEDERAL REGISTER of May 15, 1973 (38 FR 12738).

Accordingly, the Commissioner has concluded that regulations based upon the review of GRAS and prior-sanctioned direct human food ingredients will initially be proposed on the assumption that no prior sanction exists. Because prior-sanctioned status constitutes an exemption from section 409 of the Act, it should be construed narrowly, and the burden of coming forward with evidence of the sanction properly rests upon the person who asserts it. In the event that any person responds to a proposed regulation with proof of a valid prior-sanction, a final regulation will be issued under Subpart E "Substances for which prior sanctions have been granted," as well as under any other applicable sections of the regulations. In this way, all possible uses of the ingredient will be fully covered. Any regulation promulgated pursuant to this review will constitute a determination that excluded uses would result in adulteration of the food in violation of section 402 of the act, and the failure to submit proof of an applicable prior sanction in response to any proposed regulation will also constitute a waiver of the right to assert such sanction at any later point in time. Any proposed regulation will also be construed as a proposal under Subpart E in the event that a prior sanction is asserted in comments submitted on it. This procedure is necessary because of the unavailability of any comprehensive list of prior sanctions.

Methyl paraben (methyl-*p*-hydroxybenzoate) and propyl paraben (propyl-*p*-hydroxybenzoate) were listed in § 121.101(d)(2) as GRAS for use as preservatives in food at a maximum of 0.1 percent, following a proposal published in the FEDERAL REGISTER of January 31, 1961 (26 FR 938).

Methyl paraben and propyl paraben have been the subject of a search of the published scientific literature from 1920 to the present. The parameters used in the search were chosen to discover any articles that considered (1) the chemical toxicity, (2) occupation hazards, (3) metabolism, (4) reaction products, (5) degradation products, (6) any reported carcinogenicity, teratogenicity, or mutagenicity, (7) dose response, (8) reproductive effects, (9) histology, (10) embryology, (11) behavioral effects, (12) detection methodology, and (13) processing. A total of 325 abstracts on the parabens were reviewed and 33 particularly pertinent reports from the literature survey have been summarized in a Scientific Literature Review.

A representative cross-section of food manufacturers was surveyed to determine the specific foods in which these substances were used and at what levels. Available surveys of consumer consumption were obtained and combined with the production information to obtain an estimate of the consumer exposure to methyl paraben and propyl paraben. The total methyl paraben used in food in 1970 is reported to be about 16 times that used in 1960. The total propyl paraben used in food in 1970 is reported to be about 30 times that used in 1960.

The Scientific Literature Survey shows, among other studies, the following information as summarized in the report of the Select Committee on GRAS Substances:

"Studies in rats, rabbits, dogs, cats, and man show that methyl and propyl paraben are absorbed from the gastrointestinal tract and metabolized. Neither is accumulated in the body. The major metabolites, in decreasing concentrations in the urine, are *p*-hydroxybenzoic acid and the glycine, blucuronic acid, and sulfuric acid conjugates of *p*-hydroxybenzoic acid. Most, but probably not all of the ingested parabens, is metabolized to the foregoing substances through normal pathways in the liver and kidneys. The following work is particularly significant.

In rabbits, 86 percent of a single 400 mg or 800 mg dose of methyl paraben was excreted within 24 hours as *p*-hydroxybenzoic acid (39 percent), hippuric acid (15 percent), the glucuronic ester and ether (22 percent), and sulfuric acid conjugates (10 percent). In rabbits, 70 percent of a single 400 mg dose of propyl paraben was excreted as the same metabolites within 9 hours, 85 percent within 24 hours, and 88 percent within 48 hours.

In dogs, 66 percent of a 1.0 g per kg oral dose of methyl paraben was excreted within 24 hours (89 percent within 48 hours) as *p*-hydroxybenzoic acid and glucuronic acid conjugates. No accumulation of either methyl or propyl paraben was observed when 1.0 g per kg was administered daily for one year; the rate of excretion of the administered dose increased to 96 percent each 24 hours during that period.

In a fasted man, 50 percent of a dose of 70 mg per kg of methyl paraben was excreted as *p*-hydroxybenzoic acid and conjugates with-

in 12 hours. In another human subject, 55 percent of a daily 2.0 g dose of propyl paraben was excreted as sulfuric acid conjugates. Inasmuch as the authors were unable to account for all of the administered paraben as the foregoing excretion products, it was concluded that some cleavage of the benzene ring may occur metabolically.

Relevant short-term animals studies (extending for less than half of the life span of the species) and studies on man are summarized below. There is a dearth of closely controlled experimental data.

The oral LD_{50} of both methyl paraben and propyl paraben for the mouse is reported to be greater than 8,000 mg per kg. The oral LD_{100} of methyl paraben is reported to be 3,000 mg per kg for the rabbit and 2,000 mg per kg for the dog; that for propyl paraben is 6,000 mg per kg for the rabbit and 3,000 to 4,000 mg per kg for the dog.

Dogs fed as much as 1,000 mg per kg per day of methyl or propyl paraben six days weekly for one year exhibited no toxic symptoms, and blood samples were normal. One female that had been receiving 500 mg per kg per day of methyl paraben for one year was mated and delivered a litter of healthy pups. In other experiments, two dogs were unaffected by oral methyl or propyl paraben levels of 500 mg per kg per day, but evidence of toxicity appeared at 2,000 mg per kg per day of methyl paraben and at 4,000 mg per kg per day of propyl paraben.

Growth of young rats, thought at first to be retarded by oral doses of 250 and 500 mg per kg per day of methyl paraben (period of feeding not reported), was found to be unaffected when these experiments were 'extensively repeated'.

Rabbits fed methyl or propyl paraben at 500 mg per kg per day for 6 days showed no ill effects. With both compounds, first distinct toxic effects were reported to appear when fed at 3,000 mg per kg per day.

A human volunteer, ingesting 2,000 mg of methyl paraben daily for one month was unaffected. Similarly, a human volunteer ingesting 2,000 mg of propyl paraben daily for one month exhibited no visible toxic effects. One experimenter reported that he ingested 2,000 mg of methyl paraben daily for an unstated period and "was able to ascertain an innocuousness even with prolonged use and in doses considerably greater than the minimum necessary in its practical application".

Methyl paraben elicited no teratogenic response in pregnant mice or rats fed up to 550 mg per kg daily for 10 consecutive days, or in pregnant hamsters fed up to 300 mg per kg daily for 5 consecutive days.

Methyl paraben or propyl paraben, dissolved in propylene glycol and applied to the skin of 50 human subjects every other day for 10 applications, produced no irritation at the 5 percent level (methyl) or 12 percent level (propyl). In man, 0.1 to 0.3 percent aqueous solutions of methyl paraben, instilled into the eyes of more than 100 patients, produced moderate hyperemia, slight lacrimation, and a sensation of burning which disappeared within one minute. Repetition of this procedure several times a day resulted in no complaints from the 100 subjects. It was noted in 1969 that eight cases of contact dermatitis due to the parabens had been reported in the U.S. scientific literature.

The following long-term studies of the feeding of the parabens are relevant.

Weanling Wistar rats, fed 0.9 to 1.2 g per kg per day for 96 weeks of either methyl or propyl paraben, remained indistinguishable from the controls. Autopsies revealed no pathology in kidney, liver, heart, lung, spleen, or pancreas. When dosage of either compound was increased about four times, rats showed a slower rate of weight gain than the controls. The authors estimated that the toxic threshold for rats of both methyl and propyl paraben is at least 3,000 mg per kg per day. In mice, the same authors stated, "the doses required to produce toxic effects are so large as to make it difficult to obtain an entirely satisfactory dosage-response curve".

Propyl paraben, fed to rats over an 18 month period at 150 mg per kg per day, resulted in no ill effects and 'some evidence of growth stimulation'. When fed at a level of 1,500 mg per kg per day there was a decrease in growth rate, 'but no irregular pathological changes could be found.' No experiments were reported for methyl paraben, but ethyl paraben, fed at the foregoing levels paralleled the experience with propyl paraben. In another study, weanling rats, fed as much as 1,430 mg per kg per day of a mixture of 60 parts propyl paraben and 40 parts ethyl paraben for 18 months, showed growth rates comparable to the controls and histological examination revealed no significant pathological differences among the test and control rats.

No oral carcinogenicity studies of the parabens have been reported. There are two reports of carcinogenicity studies by other routes of paraben administration. Methyl paraben, dissolved in polyethylene glycol and introduced twice weekly into the vaginas of weanling mice for 18 months, did not initiate carcinomas. In other tests on mice, methyl paraben administered intravenously or subcutaneously exhibited no carcinogenic activity.

The available information reveals that there are no short-term toxicological consequences in the rat, rabbit, cat, dog, or man, and no long-term toxicological consequences in rats, of consuming the parabens in amounts greatly exceeding those currently consumed in the normal diet of the U.S. population. There is no evidence that consumption of the parabens as food ingredients has had an adverse effect on man in the 40 years they have been so used in the United States.

All of the available safety information has been carefully evaluated by qualified scientists of the Select Committee on GRAS Substances selected by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology (FASEB). It is the opinion of the Select Committee that there is no evidence in the available information on methyl and propyl paraben that demonstrates a hazard to the public when they are used at current levels or at levels that may reasonably be expected in the future. Based upon his own evaluation of this information, the Commissioner concurs with this conclusion.

Copies of the Scientific Literature Review on the parabens, the data on the teratology experiments, and the report of the FASEB Committee are available for review at the office of the Hearing Clerk, Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20852, and may be purchased from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22151.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409(d), 701(a), 52 Stat. 1055, 72 Stat. 1787; 21 U.S.C. 321(s), 348(d), 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes that Part 121 be amended as follows:

§ 121.101 [Amended]

1. By revising the introductory text of § 121.101(d) to read as follows:

Substances that are generally recognized as safe for their intended use within the meaning of section 409 of the act are as follows. When the status of a substance has been reevaluated and affirmed as GRAS or delisted from this paragraph, an appropriate explanation will be noted, e.g., "affirmed as GRAS," "food additive regulation," "interim food additive regulation," or "prohibited from use in food," with a reference to the appropriate new regulation. Such notation will apply only to the specific use covered by the review, e.g., direct human food use and/or indirect human food use and/or animal feed and pet food use, and will not affect its status for other uses not specified in the referenced regulation pending a specific review of such other uses.

2. By amending the heading for the column "Limitations or restrictions" in § 121.101(d) to read "Limitations, restrictions or explanations", and by amending subparagraph (2) of paragraph (d) by revising the text in the "Limitations, restrictions or explanations" column for the items "Methyl parabren (methy-p-hydroxybenzoate)" and "Propyl paraben (propyl-p-hyroxybenzoate)" to read as follows:

§ 121.101 Substances that are generally recognized as safe.

* * * * *

(d) * * *

Product	Tolerance	Limitations, restrictions or explanations
* * *	* * *	* * *
Methyl paraben (methyl-p-hydroxybenzoate).	0.1 percent	Affirmed as GRAS § 121.104(g)(1).
* * *	* * *	* * *
Propyl paraben (propyl-p-hydroxybenzoate).	0.1 percent	Affirmed as GRAS § 121.104(g)(2).
* * *	* * *	* * *

3. By adding a new section to Subpart B as follows:

§ 121.104 Substances added directly to human food affirmed as generally recognized as safe (GRAS).

(a) The direct human food ingredients listed in this section have been reviewed by the Food and Drug Administration and determined to be generally recognized as safe (GRAS) for the purposes and under the conditions prescribed.

(b) Any use levels included in this section represent maximum use levels under current good manufacturing practices. This section does not authorize addition of any level of an ingredient to a specific food above the amount reasonably necessary to accomplish the intended effect.

(c) The listing of a food ingredient in this section does not authorize the use of such substance in a manner that may lead to deception of the consumer or to any other violation of the act.

(d) The listing of more than one ingredient to produce the same technological effect does not authorize use of a combination of two or more ingredients to accomplish the same technological effect in any one food at a combined level greater than the highest level permitted for one of the ingredients.

(e) If the Commissioner of Food and Drugs is aware of any prior sanction for use of an ingredient under conditions different from those proposed to be affirmed as GRAS, he will concurrently propose a separate regulation covering such use of the ingredient under Subpart E of this part. If the Commissioner is unaware of any such applicable prior sanction, the proposed regulation will so state and will require any person who intends to assert or rely on such sanction to submit proof of its existence. Any regulation promulgated pursuant to this section constitutes a determination that excluded uses would result in adulteration of the food in violation of section 402 of the Act, and the failure of any person to come forward with proof of such an applicable prior sanction in response to the proposal will constitute a waiver of the right to assert or rely on such sanction at any later time. The notice will also constitute a proposal to establish a regulation under Subpart E, incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable prior sanction in response to the proposal.

(f) The label and labeling of the ingredient and any intermediate mix of the ingredient for use in finished food shall bear, in addition to the other labeling required by the act:

(1) The name of the ingredient.

(2) A statement of the concentration of the ingredient in any intermediate mix.

(3) Adequate information to assure that the final food product may comply within any limitations prescribed for the ingredient.

(g) The following direct human food ingredients have been affirmed as GRAS:

(1) *Methyl paraben.* (i) Methyl paraben is the chemical methyl-*p*-hydroxybenzoate, produced by esterification of *p*-hydroxybenzoic acid.

(ii) The ingredient meets the specification of the Food Chemicals Codex 2nd Ed. (1972).[1]

(iii) The ingredient is used as a preservative.

(iv) The ingredient is used in food at levels not to exceed good manufacturing practices. Current good manufacturing practice results in a maximum level of 0.1 percent in food.

(2) *Propyl paraben.* (i) Propyl paraben is the chemical propyl-*p*-hydroxybenzoate, produced by esterification of *p*-hydroxybenzoic acid.

(ii) The ingredient meets the specification of the Food Chemicals Codex 2nd Ed. (1972).

(iii) The ingredient is used as a preservative.

(iv) The ingredient is used in food at levels not to exceed good manufacturing practices. Current good manufacturing practice results in a maximum level of 0.1 percent in food.

The Commissioner hereby gives notice that he is unaware of any prior sanction for the use of these ingredients in food under conditions different from the proposed above. Any person who intends to assert or rely on such a sanction shall submit proof of its existence in response to this proposal. The regulations proposed above will constitute a determination that excluded uses would result in adulteration of the food in violation of section 402 of the Act, and the failure of any person to come forward with proof of such an applicable prior sanction in response to this proposal constitutes a waiver of the right to assert or rely on such sanction at any later time. This notice also constitutes a proposal to establish a regulation under Subpart E, incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable prior sanction in response to this proposal.

Interested persons may, on or before October 24, 1973, file with the Hearing Clerk, Food and Drug Administration, Room 6–88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: July 19, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73–15212 Filed 7–25–73;8:45 am]

[1] Copies may be obtained from: National Academy of Sciences 2101 Constitution Ave., NW Washington, DC 20037.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

GRAS OR PRIOR-SANCTIONED DIRECT HUMAN FOOD INGREDIENTS

Notice of Opportunity To Submit Unpublished Safety Data

The Food and Drug Administration is conducting a study of the direct human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. As part of this study, information on each ingredient (or group of ingredients) is being summarized in a series of Scientific Literature Reviews by organizations under contract with the Food and Drug Administration. The organizations preparing the Scientific Literature Reviews are responsible for including a summary of the world literature on safety published since January 1, 1920.

In order to assure that all pertinent safety information is obtained for inclusion in each Scientific Literature Review, this notice solicits from any source unpublished data and information that may be appropriate in determining the safety of the substances. The organizations preparing the Scientific Literature Reviews, and the Reviews now in active preparation or planned for preparation, are as follows:

1. Food and Drug Research Laboratories, Inc.,
   60 Evergreen Place,
   East Orange, NJ 07018.
2. Franklin Institute Research Laboratories,
   The Benjamin Franklin Parkway,
   Philadelphia, PA 19103.
3. Informatics, Inc.,
   6000 Executive Boulevard,
   Rockville, MD 20852.
4. Tractor Jitco, Inc.,
   1300 East Gude Dr.,
   Rockville, MD 20851.

Ingredients	Organizations	Estimated date of completion
Aluminum compounds.	Tracor Jitco, Inc.	June 29, 1973
Silicates	do	July 27, 1973
Magnesium salts	do	July 20, 1973
Manganese salts	do	Aug. 3, 1973
Starter distillate	do	Oct. 19, 1973
Acetic acid & derivatives.	do	Aug. 10, 1973
Formic acid & derivatives.	do	Aug. 31, 1973
Methyl & ethyl acrylate.	do	Oct. 19, 1973
Hydrosulfites	do	July 20, 1973
Salts of fatty acids	do	July 27, 1973
Sodium and potassium hydroxides.	do	Oct. 5, 1973
Vitamin D	do	Sept. 7, 1973
Corn silk	do	Oct. 5, 1973
Sulfamic acid	do	July 13, 1973
Tall oil	do	July 27, 1973
Fish oil, hydrogenated.	do	Aug. 24, 1973
Soy bean oil, hydrogenated.	do	Do.
Glutamic acid and derivatives.	do	June 29, 1973
Cholic acid & derivatives.	Informatics, Inc.	June 22, 1973
Calcium sequestrants	do	Do.
Choline salts	do	Do.
Algae	do	Do.
Iodine salts used in foods.	do	Do.
Pulps	do	Do.
Aconitic acid	do	Do.
Corn sugar-syrup	do	July 2, 1973
Sorbase	do	Do.
Tannic acid	do	July 9, 1973
Inositol	do	July 18, 1973
Gelatin	do	July 25, 1973
Tallow	do	Aug. 15, 1973
Succinic acid	do	Do.
Beeswax and japan wax.	Franklin Research Institute.	June 29, 1973
Carnauba wax	do	Do.
Sodium thiosulfate	do	July 30, 1973
Citrates	Food and Drug Research Labs, Inc.	June 29, 1973
Calcium oxide & calcium hydroxide.	do	Do.
Sorbates	do	Do.
Butylated hydroxyanisole.	do	Do.
Malic acid	do	Do.
Ascorbates	do	July 7, 1973
Propionates	do	July 20, 1973
Gluconate radical	do	Aug. 3, 1973
Dextrins	do	Aug. 10, 1973
Pantothenates	do	Do.
Soy protein isolated	do	Aug. 18, 1973
Rennet	do	Do.
Copper salts used in foods.	do	Aug. 24, 1973
Hydrochloric acid	do	Do.
Tartaric acid & tartrates.	do	Aug. 31, 1973
Lard & lard oil	do	Do.
Bentonite & clay	do	Sept. 7, 1973
Papain	do	Sept. 14, 1973
Gases used in foods	do	Do.
Starches	do	Sept. 21, 1973
Hydrogen peroxide	do	Do.
Carbon dioxide	do	Sept. 28, 1973
Lactic acid & derivatives.	do	Do.
Vitamin A	do	Do.

In addition, the Flavor and Extract Manufacturer's Association, 1001 Connecticut Avenue, NW., Wash., DC 20036, is preparing a Scientific Literature Review on the following 276 aliphatic alcohols, acids, aldehydes, and esters, used as flavor ingredients. The Reviews are scheduled for completion by December 15, 1973.

Aliphatic Alcohols

Linear Saturated

Amyl alcohol
Butyl alcohol
1-Decanol
Ethyl alcohol
Heptyl alcohol
1-Hexadecanol
Hexyl alcohol
Lauryl alcohol
Nonyl alcohol
1-Octanol
Propyl alcohol
Undecyl alcohol

Linear Unsaturated

2-Hexen-1-ol
3-Hexen-1-ol
2,6-Nonadien-1-ol
trans-2-Nonen-1-ol

Branched Saturated

iso-Amyl alcohol
iso-Butyl alcohol
3,7-Dimethyl-1-octanol
2-Ethyl-1-hexanol
3,5,5-Trimethyl-1-hexanol

Branched Unsaturated

Geranol
Critronellol
Nerol
Rhodinol
Farnesol

Aliphatic Acids

Linear Saturated

Acetic acid
Butyric acid
Decanoic acid
Formic acid
Hexanoic acid
Lauric acid
Myristic acid
Nonanoic acid
Octanoic acid
Palmitic acid
Propionic acid
Stearic acid
Valeric acid
Undecanoic acid
Heptanoic acid

Linear Unsaturated

Oleic acid
4-Pentenoic acid
trans-2-Hexenoic acid
3-Hexenoic acid
10-Undecenoic acid
9, 12-Octadecadienoic acid (48%) and
9, 12, 15-Octadecatrienoic acid (52%)

Branched Saturated

iso-Butyric acid
2-Ethylbutyric acid
2-Methylbutyric acid
2-Methylhexanoic acid
2-Methylheptanoic acid
2-Methylvaleric acid
iso-Valeric acid

Branched Unsaturated

3,7-Dimethyl-6-octenoic acid
3-Methylcrotonic acid
2-Methyl-2-pentenoic acid
2,3-Dionethyl-2-pentenoic acid

Aliphatic Aldehydes

Linear Saturated

Acetaldehyde
Butyraldehyde
Decanal
Heptanal
Hexanal
Lauric aldehyde
Myristaldehyde
Nonanal
Octanal
Propionaldehyde
Undecanal
Valeraldehyde

Linear Unsaturated

cis-3-Hexenal
10-Undecenal
9-Undecenal
4-Heptenal
4-Decenal

Conjugated

2-Decenal
2-Dodecenal
2-Heptenal
2,4-Nonadienal
2-Hexenal
2-Tridecenal
2-*trans*, 4-*trans*-Decadienal
2,4-Heptadienal
2-Nonenal
2-Octenal
2,4-Pentadienal
2-Pentenal
Nona-2-*trans*, 6-*cis*-Dienal

Branched Saturated

iso-Butyraldehyde
2,6-Dimethyl octanal
2-Methylbutyraldehyde
3-Methylbutyraldehyde
2-Ethylbutyraldehyde
2-Methyloctanal
2-Methylundecanal

BRANCHED UNSATURATED

Citronellal
2,6-Dimethyl-5-heptenal

CONJUGATED

Citral
2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal
2-Ethyl-2-heptenal
2-Methyl-2-pentenal

ALIPHATIC ESTERS

(with linear saturated acid portion and alcohol portion as indicated)

LINEAR SATURATED

Amyl butyrate
Amyl heptanoate
Amyl octanoate
Butyl butyrate
Butyl heptanoate
Butyl laurate
Butyl stearate
Decyl acetate
Decyl propionate
Ethyl butyrate
Amyl formate
Amyl hexanoate
Butyl acetate
Butyl formate
Butyl hexanoate
Butyl propionate
Butyl valerate
Decyl butyrate
Ethyl acetate
Ethyl decanoate
Ethyl formate
Ethyl hexanoate
Ethyl myristate
Ethyl octadecanoate
Ethyl palmitate
Ethyl undecanoate
Heptyl acetate
Heptyl formate
Hexyl acetate
Hexyl formate
Hexyl octanoate
Lauryl acetate
Methyl butyrate
Methyl hexanoate
Methyl myristate
Methyl octanoate
Methyl valerate
Nonyl octanoate
Octyl butyrate
Octyl heptanoate
Octyl propionate
Propyl butyrate
Propyl heptanoate
Propyl propionate
Ethyl heptanoate
Ethyl laurate
Ethyl nonanoate
Ethyl octanoate
Ethyl propionate
Ethyl valerate
Heptyl butyrate
Heptyl octanoate
Hexyl butyrate
Hexyl hexanoate
Hexyl propionate
Methyl acetate
Methyl heptanoate
Methyl laurate
Methyl nonanoate
Methyl propionate
Nonyl acetate
Octyl acetate
Octyl formate
Octyl octanoate
Propyl acetate
Propyl formate
Propyl hexanoate

LINEAR UNSATURATED

Allyl butyrate
Allyl hexanoate
Allyl octanoate
2-Hexen-1-yl acetate
cis-3-Hexen-1-yl acetate
Allyl heptanoate
Allyl nonanoate
Allyl propionate
10-Undecen-1-yl acetate
3-Hexenyl formate

BRANCH SATURATED

iso-Amyl acetate
iso-Amyl formate
iso-Amyl laurate
iso-Amyl octanoate
iso-Butyl acetate
iso-Butyl formate
iso-Butyl hexanoate
2-Ethyl butyl acetate
iso-Amyl butyrate
iso-Amyl hexanoate
iso-Amyl nonanoate
iso-Amyl propionate
iso-Butyl butyrate
iso-Butyl heptanoate
iso-Butyl propionate

BRANCH UNSATURATED

Citronellyl acetate
Citronellyl formate
Citronellyl valerate
Geranyl butyrate
Geranyl hexanoate
Citronellyl butyrate
Citronellyl propionate
Geranyl acetate
Geranyl formate
Geranyl propionate

ALIPHATIC ESTERS

(with linear unsaturated acid portion and alcohol portion as indicated)

LINEAR SATURATED

Butyl 2-decenoate
Ethyl acrylate
Ethyl 2-nonynoate
Ethyl sorbate
Methyl 2-hexenoate
Methyl 2-nonynoate
Methyl 9-undecenoate
Ethyl *trans*-2, *cis*-4-Decadienoate
Ethyl *cis*-4-octenoate
Methyl 3-hexenoate
Butyl 10-undecenoate
Ethyl crotonate
Ethyl oleate
Ethyl 10-undecenoate
Methyl 2-nonenoate
Methyl 2-octynoate
Methyl 2-undecynoate
Ethyl 3-hexenoate
n-Hexyl 2-butenoate
Methyl *cis*-4-ctenoate

LINEAR UNSATURATED

Allyl sorbate
2-Methylallyl butyrate
Neryl butyrate
Neryl propionate
Rhodinyl butyrate
Rhodinyl propionate
Allyl 10-undecenoate
Neryl acetate
Neryl formate
Rhodinyl acetate
Rhodinyl formate

ALIPHATIC ESTERS

(with branched saturated acid portion and alcohol portion as indicated)

LINEAR SATURATED

Butyl *iso*-Butyrate
Butyl *iso*-Valerate
Ethyl *iso*-Butyrate
Ethyl *iso*-Valerate
Hexyl *iso*-Valerate
Methyl 2-Methylbutyrate
Methyl *iso*-Valerate
Octyl *iso*-Butyrate
Propyl *iso*-Butyrate
Hexyl *iso*-Butyrate
Ethyl 2-Methylbutyrate
Heptyl *iso*-Butyrate
Methyl *iso*-Butyrate
Methyl 4-methylvalerate
Nonyl *iso*-Valerate
Octyl *iso*-Valerate
Propyl *iso*-Valerate

LINEAR UNSATURATED

Allyl 2-ethylbutyrate
3-Hexenyl *iso*-Valerate
Allyl *iso*-Valerate
3-Hexenyl-2-methylbutyrate

BRANCH SATURATED

Hexyl-2-methylbutyrate
iso-Amyl *iso*-Valerate
3,7-Dimethyllocta-2,6-dienyl 2-ethylbutanoate
2-Methylbutyl-*iso*-Valerate
2-Methylpropyl 3-Methylbutyrate
iso-Amyl-*iso*-Butyrate
iso-Amyl-2-methylbutyrate
2-Methylbutyl 2-methylbutyrate

BRANCH UNSATURATED

Citronellyl *iso*-Butyrate
Geranyl *iso*-Valerate
Neryl *iso*-Valerate
Rhodnyl *iso*-Valerate
Geranyl *iso*-Butyrate
Neryl *iso*-Butyrate
Rhodinyl *iso*-Butyrate

ALIPHATIC ESTERS

(with branched unsaturated acid portion and alcohol portion as indicated)

LINEAR SATURATED

Ethyl tiglate
Methyl 3,7-dimethyl-6-octenoate

LINEAR UNSATURATED

Allyl tiglate

BRANCH SATURATED

iso-Butyl angelate

The above list of 276 flavor ingredients represents the initiation of Scientific Literature Reviews of 1,550 natural and synthetic flavor substances. An announcement will be made in the FEDERAL REGISTER when other flavor compounds are selected for Review, so that appropriate unpublished information and data may be submitted. All flavor ingredients listed in §§ 121.101(e) and (g), 121.1163 and 121.1164, or otherwise submitted or known to FDA, are intended for eventual inclusion in a Scientific Literature Review.

Other GRAS and prior sanctioned food ingredients intended for an immediate or planned Scientific Literature Review are listed below under their appropriate categories.

IMMEDIATE SCIENTIFIC LITERATURE REVIEW

Adipic acid
Casein and caseinates
Hypophosphites
Pectin and pectinates
Gum guaiac
Ascorbic acid
Carotenes
Iron, reduced
Niacin and niacinamide
Pyridoxine and pyridoxine hydrochloride
Riboflavin and riboflavin-5-phosphate
Caffeine
Glycerophosphates
Dextrans

Vegetable oils
Sucrose
Biotin
Citric acid
Lecithins
Para-hydroxylbenzylisothiayanate
Thiamine
Urea
Vitamin B_{12}
Sodium and potassium chlorides

PLANNED SCIENTIFIC LITERATURE REVIEW

Amines (filming)
Benzoyl peroxide
Borax
Brandy
Calcium stearate
Carbon
Char smoke flavor
Collagen (avitene)
Cyclohexylamine
Enzymes (proteolytic)
Ferrocyanide salts
Glucono delta lactone
Glycerol lactopalmitate
Hesperidin complex
Lignin
Malt syrup
Milk powder (whole, enzyme modified)
Amino tri (methylene phosphoric acid) sodium salt
Bergamot oil
Bouillon (vegetable, smoked)
Butter fat, enzyme modified w/added butyric acid
Candelillla wax
Carboxymethyl hydroxyethyl cellulose
Chlorophyll
Corn mint oil (mentha arvenis oil)
Enzymes (bacterial)
Ferrous citrate
Furcelleran
Gluten (corn)
Gums (vegetable)
Iron citrate
Liver fractions
Methylpolysilicone
Mono and diglycerides (sodium sulfoacetate derivatives)
< Morpholine
<Nickel
< Octadecylamines
Oiticia
Peptone (pepsin-modified soy bean protein; brewers peptone)
Piperazine dihydrochloride
Potassium gluconate
Rutin
Silver-silver dragees
Sodium fluoride
Sodium metasilicate
Soya fatty acid amine (ethoxylated)
Starch (food, modified)
Vitamin B complex and syrup
Yeasts
Pepsin
Potassium bromate
Potassium phosphates
Sausage casings (HCl and cellulose fibers)
Sodium chlorite
Sodium hypochlorite
Sodium zinc metasilicate
Stearyl alcohol
Wax (shellac)
Zein powder

To be considered for inclusion in a Scientific Literature Review, two copies of all relevant safety data, and information shall be submitted to the organization preparing the Review before the listed completion date, and the original and two copies of all such information shall simultaneously be sent to GRAS Review Branch (BF-335), Bureau of Foods, Food and Drug Administration, 200 "C" Street SW., Wash., DC 20204. Immediately upon receipt of any such submission, one copy will be placed on display at the Office of the Hearing Clerk, Food and Drug Administration, Rm. 6-88, 5600 Fishers Lane, Rockville, MD 20852, where it may be reviewed during working hours, Monday through Friday.

If the contractor has not been named, the original and four copies of any such data and information shall be submitted to the GRAS Review Branch (address above), which will distribute two copies to the contractor for the Scientific Literature Review when he is selected. A copy of all such submissions will also immediately be placed on display at the office of the Hearing Clerk, at the above address.

If the estimated date of completion of the Review has passed, copies of any such safety data and information shall be submitted to the Select Committee on GRAS Substances and the GRAS Review Branch as provided by the notice published elsewhere in this issue of the FEDERAL REGISTER, and a copy of any such submission will immediately be placed on display at the office of the Hearing Clerk pursuant to that notice.

Dated: July 19, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73-15220 Filed 7-25-73;8:45 am]

SAFETY OF GRAS AND PRIOR-SANCTIONED DIRECT HUMAN FOOD INGREDIENTS

Notice of Opportunity To Present Data Information and Views

The Food and Drug Administration is conducting a study of the safety of direct human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. As part of this study, information on each such ingredient (or group of ingredients), gathered from literature searches and other sources, is being summarized in a series of written Scientific Literature Reviews by organizations under contract with the Food and Drug Administration. The organizations preparing the Scientific Literature Reviews are responsible for including a summary of the world literature on safety published since January 1, 1920. Opportunity is provided, elsewhere in this issue of the FEDERAL REGISTER, for any interested person to submit unpublished safety data and information on these food ingredients for inclusion in Scientific Literature Reviews now under preparation.

Several Scientific Literature Reviews have now been completed and submitted to the Food and Drug Administration. A list of those completed Reviews appears elsewhere in this issue of the FEDERAL REGISTER, (38 FR), and notice is given of their public availability.

The Food and Drug Administration briefly examines each Scientific Literature Review before accepting it. This brief examination covers only the general quality of the work, to make certain that the major scientific information is included in a balanced and complete presentation. The examination is not intended to determine that all pertinent scientific information is included. Notice is therefore hereby given that any interested person who, after study of a Scientific Literature Review, believes that additional pertinent published or unpublished data or information should be included in considering the safety of the ingredient(s) covered in the Scientific Literature Review, may submit ten copies of such written data, information, or views to:

Select Committee on GRAS Substances,
Federation of American Societies for Experimental Biology,
9650 Rockville Pike,
Bethesda, MD 20014

The original of this material and two additional copies shall simultaneously be sent to:

Bureau of Foods,
Food and Drug Administration,
GRAS Review Branch (BF-335),
200 "C" Street, S.W.,
Washington, DC. 20204.

Immediately upon receipt, one copy of any such submission will be placed on display at the office of the Hearing Clerk, Food and Drug Administration, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852, where it may be reviewed during working hours, Monday through Friday.

The Select Committee on GRAS Substances is utilizing the services of special consultants with particular expertise in considering specific issues that arise in the evaluation of these substances. The Select Committee also recognizes that the presentation of oral views with respect to the safety of these substances may be helpful in its work. Therefore, an opportunity will be provided for any interested person to present oral views on the safety of these substances to the Select Committee at a hearing, as part of the evaluation process. Notices providing an opportunity to participate in a hearing, for the presentation of such oral views to the Select Committee, will be published in the FEDERAL REGISTER at the appropriate time.

Following completion of its evaluation, the Select Committee will prepare a report to the Commissioner of Food and Drugs containing its evaluation and recommendations, with respect to the safety of the particular ingredient(s) covered by a Scientific Literature Review. Upon acceptance of the report by the Food and Drug Administration, it will be made available to the public in accordance with the notice on this matter published elsewhere in this issue of the FEDERAL REGISTER. After evaluating this report, the Commissioner will publish in the FEDERAL REGISTER, an appropriate proposal to (1) affirm GRAS status, (2) publish a prior sanction, (3) establish an interim food additive regulation, (4) establish a permanent food additive regulation, or (5) eliminate food use of the ingredient. These proposals will be issued pursuant to the procedural provisions contained in §§ 121.40, 121.41 published in the FED-

ERAL REGISTER of December 2, 1972 (37 FR 25705), and § 121.2000 published in the FEDERAL REGISTER of May 15, 1973 (38 FR 12737). The Commissioner is proposing elsewhere in this issue of the FEDERAL REGISTER, to establish new §§ 121.104 *Substances added directly to human food affirmed as generally recognized as safe (GRAS)*, 121.105 *Substances in food contact surfaces affirmed as generally recognized as safe (GRAS)*, and 121.106 *Substances prohibited from use in food.* Thus, each food ingredient will be proposed for inclusion in one of these three new sections, in Subpart D (direct human food additives), in Subpart E (prior sanctions), in Subpart F (indirect human food additives), or in Subpart H (interim human food additives).

Following publication of any such proposal, all interested persons will have an opportunity to submit written comments on the proposal. Where good cause is shown, the Commissioner may order a public hearing at which an oral presentation of data, information, and views may be made. The final regulation will be final agency action from which appeal lies to the courts.

The Commissioner urges the cooperation of all segments of the public in this important work.

Dated: July 19, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73-15221 Filed 7-25-73;8:45 am]

SELECT COMMITTEE ON GRAS SUBSTANCES

Request for Nominations

The Food and Drug Administration is conducting a study of direct human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. The available information relating to the safety of each such ingredient is first being evaluated by a Select Committee on GRAS Substances selected by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology under a contract with the Food and Drug Administration. The Select Committee is considering information on GRAS substances provided by a series of Scientific Literature Reviews based primarily upon a literature survey of material published from 1920 to 1973, by current production and consumption patterns obtained from a recent survey by the National Academy of Sciences, and by additional recent toxicological screening tests on certain of the substances. The Select Committee is presently comprised of the following individuals:

1. Dr. Bert N. Ladu, Jr.,
Dept. of Pharmacology,
New York University Medical Center.
New York University School of Medicine,
550 1st Ave.,
New York University Medical Center,
2. Dr. John R. McCoy,
Professor of Comparative Pathology,
New Jersey College of Medicine & Dentistry,
Rutgers Medical School,
P.O. Box 2100,
New Brunswick, NJ 08903.
3. Dr. Aaron M. Altschul,
Dept. of Community Medicine & International Health,
School of Medicine,
Georgetown University,
3750 Reservoir Road, NW.,
Wash., DC 20007.
4. Dr. Joseph F. Borzelleca,
Professor of Pharmacology,
Medical College of Virginia,
Health Sciences Division,
Virginia Commonwealth University,
Richmond, VA 23219.
5. Dr. Sanford A. Miller,
Dept. of Nutrition and Food Science,
Rm. E 18-564,
Massachusetts Institute of Technology,
Cambridge, MA 02139.
6. Dr. Ralph G. H. Siu,
Consultant,
4428 Albemarle St., NW.,
Wash., DC 20016.
7. Dr. John L. Wood,
University of Tennessee Medical Units,
62 S. Dunlap St.,
Memphis, TN 38103.
8. Dr. Gabriel L. Plaa,
Dept. of Pharmacology,
University of Montreal,
Faculty of Medicine,
Case Postale 6128,
Montreal 101, Que., Canada.
9. Dr. George W. Irving, Jr., Chairman,
Research Associate,
Life Sciences Research Office,
Federation of American Societies for Experimental Biology,
9650 Rockville Pike,
Bethesda, MD 20014.

The curriculum vitae of each member of the Select Committee is available for public review at the office of the Hearing Clerk, Food and Drug Administration, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852.

The Life Sciences Research Office plans to increase the size of the Select Committee working on this project. Accordingly, notice is hereby provided for all interested parties to nominate additional qualified scientists to serve on the Select Committee. Nominations are invited from individuals and from consumer, industry, and professional organizations, and should be sent to:

Dr. C. Jelleff Carr,
Life Sciences Research Office,
Federation of American Societies for Experimental Biology,
9650 Rockville Pike,
Bethesda, MD 20014.

Nominations must state that the person nominated is aware of the nomination, is interested in becoming involved in this effort, and appears to have no conflict of interest. A complete curriculum vitae must be enclosed with each nomination.

Dated: July 19, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73-15219 Filed 7-25-73;8:45 am]

STATUS OF REVIEW OF GRAS AND PRIOR-SANCTIONED DIRECT HUMAN FOOD INGREDIENTS

Notice of Availability of Information

Food ingredients that are generally recognized as safe (GRAS), or that were sanctioned through action by the Food and Drug Administration or the United States Department of Agriculture prior to enactment of the Food Additives Amendment of 1958, may be utilized in food without first obtaining approval through a food additive regulation. After enactment of the law, the Food and Drug Administration published a partial list of GRAS and prior-sanctioned ingredients in § 121.101. This list was developed without a thorough scientific review of each ingredient.

In his Consumer Message of October 30, 1969, President Nixon directed the Secretary of Health, Education, and Welfare to initiate a full review of all GRAS ingredients. To implement this mandate, the Food and Drug Administration contracted with the Food Protection Committee of the National Academy of Sciences to survey the entire food industry to determine the national production of all GRAS ingredients and the amount of each such ingredient used in any particular food. The National Academy of Sciences report to the Food and Drug Administration incorporated the results of independent surveys conducted by the United States Department of Agriculture as part of its 1965 Household Food Consumption surveys to determine the sizes of food servings used by consumers, and by the Market Research Corporation of America, to determine how frequently representative consumers eat individual servings of foods in specific food categories. The results of the NAS Survey, describing incorporation of USDA and MRCA data, is now available. The complete Survey report also contains various tabular computer printouts describing the use of GRAS food ingredients in NAS food categories and the total exposure of GRAS food ingredients in human foods.

The Food and Drug Administration also contracted with the Franklin Institute Research Laboratories, The Benjamin Franklin Parkway, Philadelphia, PA 19103, to conduct a search of the world literature since January 1, 1920 on the following 72 GRAS food ingredients that were determined to be a matter of high priority:

Ammoniated glycyrrhizin
Sodium nitrite
Sodium nitrate
Potassium nitrate
Potassium nitrite
Saccharin (acid)
Sodium saccharin
Calcium saccharin
Ammonium saccharin
Potassium bisulfite
Potassium metabisulfite
Sodium bisulfite
Sodium metabisulfite
Sulfur dioxide
Oil of mustard

Oil of garlic
Oil of nutmeg
Oil of rue
Oil of clove
Caramel
Benzoic acid
Sodium benzoate
Methyl paraben
Propyl paraben
Propyl gallate
Carrageenan
Sodium alginate
Gun tragacanth
Gum arabic (acacia)
Carob bean gum
Ghatti gum
Sterculia gum
Guar gum
Furcelleran
Sodium carrageenan
Sorbitol
Mannitol
Butylated hydroxyanisole
Butylated hydroxytoluene
Hydrogen peroxide
Diacety tartaric acid esters of mono- and diglycerides of edible fats and oils, or edible fat-forming acids
Stannous chloride
Diacetyl
Monosodium glutamate
Monopotassium glutamate
Glutamic acid
Glutamic acid hydrochloride
Monoammonium glutamate
Zinc sulfate
Zinc gluconate
Sodium thiosulfate
Dilauryl thiodipropionate
Thiodipropionic acid
Calcium propionate
Bentonite
Carnauba wax
Sodium aluminosilicate
Tricalcium silicate
Vitamin A
Vitamin A acetate
Vitamin A palmitate
Vitamin D_2
Vitamin D_3
Zinc chloride
Zinc oxide
Zinc stearate
Aluminum calcium silicate
Calcium silicate
Magnesium silicate
Sodium calcium aluminosilicate, hydrated

This literature search is being expanded to include all of the GRAS substances for direct human food use included in § 121.101(d) and a number of substances possessing such GRAS status by virtue of a communication from the Food and Drug Administration. A complete list of these substances, and their scheduled coverage by Scientific Literature Reviews, is included in a notice published elsewhere in this issue of the FEDERAL REGISTER.

Each scientific literature search is designed to discover any articles that considered (1) chemical toxicity, (2) occupational hazards, (3) metabolism, (4) reaction products, (5) degradation products, (6) reported carcinogenicity, teratogenicity, or mutagenicity, (7) dose response, (8) reproductive effects, (9) histology, (10) embryology, (11) behavioral effects, (12) detection methodology, and (13) processing. The results of this search are then incorporated in a Scientific Literature Review on each ingredient (or group of chemically similar ingredients).

Additional toxicological screening tests were conducted on 42 selected GRAS ingredients for mutagenisis and teratology. Teratological screening was conducted on all 42 ingredients in four mammalian species: Rat, mouse, hamster, and rabbit. Chick embryo tests were also conducted on 41 of those ingredients. The mutogenic test conducted on 40 of the ingredients, used the host mediated assay, the dominant lethal, and the cytogenic assay procedures. These studies were designed primarily to evaluate these relatively new toxicological screening tests, and an assessment of their value is not yet possible.

The Food and Drug Administration then contracted with the Federation of American Societies for Experimental Biology (FASEB) to conduct the initial evaluation of the Scientific Literature Reviews, the NAS production and consumption data, and the additional toxicological test data, and to provide a report on the safety of each individual ingredient. The Life Sciences Research Office of FASEB in turn appointed a Select Committee on GRAS Substances (SCOGS) which has been working since June 1972 to conduct this evaluation. Notices appear elsewhere in this issue of the FEDERAL REGISTER requesting nominations for additional qualified scientists to serve on this Select Committee, providing an opportunity to submit unpublished safety data and information on GRAS or prior-sanctioned direct human food ingredients to the organizations preparing the Scientific Literature Reviews, and providing an opportunity to present data, information, and views on the safety of these ingredients directly to the Select Committee for their consideration in the evaluation process.

To implement the review of GRAS and prior-sanctioned direct human food ingredients, the Commissioner of Food and Drugs has published in the FEDERAL REGISTER several regulations and notices. In announcing the review of GRAS food ingredients in the FEDERAL REGISTER of December 8, 1970 (35 FR 18632), the Commissioner proposed new criteria for determining GRAS status. These criteria were promulgated in final form in the FEDERAL REGISTER of June 25, 1971 (36 FR 12084).

A notice published in the FEDERAL REGISTER of October 23, 1971 (36 FR 20546) urged that all interested persons obtain and complete the survey questionnaire being used by the National Academy of Sciences to obtain broad representative information on the production and use of direct human food ingredients that have been listed in § 121.101 as GRAS or that were subject to a prior sanction. In additional to published GRAS substances and known prior-sanctioned substances, the NAS questionnaire also requested information on direct human food ingredients used on the basis of a conclusion that they are GRAS, but which are not published in § 121.101. Neither the Food and Drug Administration study nor the NAS survey includes indirect human food ingredients or animal food ingredients.

A procedure governing affirmation of GRAS status and determination of food additive status was promulgated in the FEDERAL REGISTER for December 2, 1972 (37 FR 25705). The same FEDERAL REGISTER notice promulgated a new Subpart H to govern the promulgation of interim food additive regulations. Subpart E was amended in the FEDERAL REGISTER for May 15, 1973 (38 FR 12737) to provide for publication of all prior sanctions for food ingredients, and to permit the addition of limitations where justified by new toxicological information.

The list of direct human food ingredients published as GRAS in § 121.101 includes 533 ingredients, 261 of which are flavors. The 272 non-flavor published GRAS ingredients will be covered in 120 Scientific Literature Reviews, all of which are completed, in progress, or planned for contract, as indicated elsewhere in this issue of the FEDERAL REGISTER.

The Food and Drug Administration has contracted with the Flavor and Extract Manufacturers Association to prepare similar Scientific Literature Reviews with respect to 276 flavor substances, listed elsewhere in this issue of the FEDERAL REGISTER. Scientific Literature Reviews will then be prepared on all remaining flavor substances, including those published as GRAS in § 121.101, those published in such food additive regulations as §§ 121.1163 and 121.1164, and those used on the conclusion that they are GRAS although they are not published in § 121.101.

The next priority matter will involve additional substances subject to food additive regulations and prior sanctions. A schedule and priorities for these have not yet been determined.

Upon receiving a Report from the FASEB Select Committee evaluating the safety of an ingredient, the Commissioner, after conducting his own evaluation, will publish in the FEDERAL REGISTER an appropriate proposal to affirm GRAS status, to publish a prior sanction, to establish an interim food additive regulation, to establish a permanent food additive regulation, or to eliminate food use of the ingredient. These proposals will be published pursuant to the procedural provisions contained in §§ 121.40, 121.41, and 121.2000. The Commissioner is proposing to establish new § 121.104 *Substances added directly to human food affirmed as generally recognized as safe (GRAS)*, § 121.105 *Substances in food-contact surfaces affirmed as generally recognized as safe (GRAS)*, and § 121.106 *Substances prohibited from use in food*, elsewhere in this issue of the FEDERAL REGISTER. Thus, each of these food ingredients will be proposed for inclusion in one of these three new sections, in Subpart D (direct human food additives), in Subpart E (prior sanctions), in Subpart F (indirect human food additives), or in Subpart H (interim human food additives).

Following publication of any such proposal, all interested persons will have an opportunity to submit written comments on the proposal. Where good cause

is shown, the Commissioner may order a public hearing at which an oral presentation of data, information, and views may be made. The final regulation will be final agency action from which appeal lies to the courts.

Section 121.101 is not limited to direct human food ingredients. Many of the substances listed in § 121.101 have been regarded as GRAS for indirect food ingredient use, in or on food-contact surfaces, and for use in pet food and animal feed. Accordingly, when an ingredient listed in § 121.101 is affirmed as GRAS for direct human food use, it will be retained in § 121.101, with the explanation that it has been affirmed as GRAS, and cross-referenced to the applicable paragraph in new § 121.104. When an ingredient is transferred to an interim food additive regulation, permanent food additive regulation, or prohibited status, for direct human use, a decision will be made as to whether the ingredient may remain as GRAS for uses other than direct human food use, or should be restricted or eliminated from such uses, and § 121.101 and other applicable regulations will be amended accordingly.

In the event that additional toxicological testing is required before the ingredient may be affirmed as GRAS or approved by a permanent food additive regulation, an interim food additive regulation will be proposed (unless there is a reasonable likelihood that a health hazard exists). Pursuant to § 121.4000, use of the ingredient must cease unless an interested person satisfies the Commissioner, in writing within 60 days following the effective date of the interim food additive regulation, that studies adequate and appropriate to resolve the questions raised about the ingredient have been undertaken. The Food and Drug Administration may itself undertake such studies, but this will occur only in very rare instances, if at all. As a general rule, the Food and Drug Administration intends to institute little or no testing for the purpose of providing data necessary to justify continued marketing of food ingredients, because of its conclusion that this is properly the function of private industry.

Many of the substances published as GRAS in § 121.101, or used on a determination that they are GRAS without publication in § 121.101, were approved by the United States Department of Agriculture for use in meat or poultry, or were approved by the Food and Drug Administration for use in various foods pursuant to correspondence, food standards, regulations, informal announcements, or in other ways, prior to 1958. Thus, many of these ingredients are subject to specific prior sanctions in addition to GRAS status. No comprehensive list of such prior sanctions exists. To the extent that one of these substances is affirmed as GRAS for all prior-sanctioned uses, the fact that it may also be subject to a prior sanction is largely of historical interest and has no regulatory significance. To the extent that one of these substances is not affirmed as GRAS for all prior-sanctioned uses, any restrictions or limitations imposed upon its use could in any event also be imposed on the prior-sanctioned uses under the adulteration provisions of the Act as provided in § 121.2000, published in the FEDERAL REGISTER of May 15, 1973 (38 FR 12738).

Accordingly, the Commissioner has concluded that regulations based upon the review of GRAS and prior-sanctioned direct human food ingredients will initially be proposed on the assumption that no prior sanction exists. Because prior-sanctioned status constitutes an exemption from section 409 of the Act, it should be construed narrowly, and the burden of coming forward with evidence of the sanction properly rests upon the person who asserts it. In the event that any person responds to a proposed regulation with proof of a valid prior sanction, a final regulation will be issued under Subpart E Substances for which prior sanctions have been granted, as well under any other applicable sections of the regulations. In this way, all possible uses of the ingredient will be fully covered. Any regulation promulgated pursuant to this review will constitute a determination that excluded uses would result in adulteration of the food in violation of section 402 of the act, and failure to submit proof of an applicable prior sanction in response to any proposed regulation will also constitute a waiver of the right to assert such sanction at any later point in time. Any proposed regulation will also be construed as a proposal under Subpart E, in the event that a prior sanction is asserted in comments submitted on it. This procedure is necessary because of the unavailability of any comprehensive list of prior sanctions.

In the past, it has been customary practice for the Food and Drug Administration to issue advisory opinions that a substance is GRAS, or is subject to a prior sanction, or is not a food additive because it is used in or on food-contact surfaces and there is no detectable migration. The Commissioner has concluded that all such past correspondence is publicly available, except that trade secrets will be retained as confidential, and that all future opinions relating to GRAS or prior-sanctioned status will be issued in the form of FEDERAL REGISTER notices proposing appropriate new regulations. Opinions solely with respect to no-migration status of food-contact ingredients will continue to be handled by letter rather than by regulation because of their limited applicability, and all such correspondence will be publicly available, except that trade secrets will be retained as confidential.

The Commissioner recognizes that the data and information obtained in the process of conducting this review of direct human food ingredients is of broad interest to the public. Accordingly, this information is available for public disclosure in the following ways.

1. The report of the National Academy of Sciences on "A Comprehensive Survey of Industry on the Use of Food Chemicals Generally Recognized As Safe" (September 1972) may be purchased from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22151. This report is now available.

2. A series of computer print-outs of the combined data from the NAS, USDA, and MRCA Surveys may be purchased from NTIS. These print-outs are now available and are explained in the NAS report.

3. The reports of the 1965 USDA Survey on "Food Consumption of Households in the United States" may be purchased separately from Superintendent of Documents, U.S. Government Printing Office, Wash., D.C. 20402, order number HFCS 1965–66, Report No. 1. These documents are now available.

4. Each Scientific Literature Review may be purchased from NTIS as it becomes available. The following Scientific Literature Reviews are now available:

Review title	Ordering No.	Printed copy price
Gum Arabic (Acacia)	PB-221-201	$4.85
Butylated Hydroxytoluene	PB-221-202	4.50
Carob Bean Gum	PB-221-203	3.00
Gum Tragacanth	PB-221-204	3.00
Sterculia	PB-221-205	3.00
Carrageenan	PB-221-206	4.50
Propyl Gallate	PB-221-207	3.75
Benzoates	PB-221-208	5.45
Parabens	PB-221-209	3.75
Sorbitol	PB-221-210	4.85
Mannitol	PB-221-211	4.85
Oil of Rue	PB-221-212	3.00
Gum Ghatti	PB-221-213	3.00
Zinc Salts	PB-221-214	5.45
Oil of Mustard	PB-221-215	4.50
Guar Gum	PB-221-216	3.75
Sulfiting Agents	PB-221-217	6.00
Caramel	PB-221-218	3.75
Oil of Garlic	PB-221-219	3.75
Nitrates-Nitrites	PB-221-220	9.00
Oil of Clove	PB-221-221	3.75
Oil of Nutmeg	PB-221-222	3.00
Dill	PB-221-223	3.00
Phosphates	PB-221-224	6.00
Agar-Agar	PB-221-225	3.75
Alginates	PB-221-226	4.50
Glycerine and Glycerides	PB-221-227	6.75
Cellulose	PB-221-228	4.85
Caprylic Acid	PB-221-229	4.50
Glycyrrhiza	PB-221-230	3.75
Carbonates	PB-221-231	5.45
Stannous Chloride	PB-221-232	4.50
Propylene Glycol and Derivatives	PB-221-233	4.50
Sulfates	PB-221-234	4.85
Ammoninum Ion	PB-221-235	5.45
Iron and Iron Salts Used in Foods	PB-221-236	5.45
Tocopherols	PB-221-237	6.75

Each Scientific Literature Review may be purchased in microfiche form for $.95 with the same ordering numbers listed above.

5. Copies of each Scientific Literature Review will be placed in the Library of Congress as they become available, under the title, "Scientific Literature Reviews on GRAS Food Ingredients," L.C. Card No. 73–600105.

6. Each report to the Commissioner from the FASEB Select Committee may be purchased from NTIS as it becomes available. The following reports are now available:

Carob Bean (Locust Bean) Gum
Parabens
Sorbitol
Mannitol

7. A copy of each of the reports of the following toxicological screening tests may be purchased from NTIS:

Ingredient	Teratology	Mutagenesis
Ammoniated Glycyrrhizin	X	
Amaranth (Red No. 2)	X	X
Sodium Saccharin	X	
Calcium Saccharin	X	
Saccharin (Insoluble)	X	X
Ammonium Saccharin	X	
Sodium Nitrate	X	X
Potassium Nitrate	X	
Sodium Nitrite	X	X
Potassium Nitrite	X	
Glycine	XY	
Sodium Bisulfite	XY	
Sodium Meta-bisulfite	XY	X
Butylated Hydroxyanisole	XY	
Butylated Hydroxytoluene	XY	X
Mannitol	XY	
Sorbitol	XY	X
Sodium Thiosulfate	XY	
Stannous Chloride	XY	
Calcium Propionate	X	
Sodium Benzoate	X	
Propyl Gallate	XY	
Methyl Paraben	XY	
Dilauryithiodipropionic Acid	XY	
Calcium Silicated (Hydrated)	XY	
Sodium Carrageenan	X	
Calcium Carrageenan	X	X
Carob Bean (Locust Bean) Gum	X	X
Gum Arabic (Acacia)	X	X
Gum Tragacanth	X	
Gum Ghatti	X	X
Guar Gum	XY	X
Stereulia (Karaya) Gum	XY	X
Propyiene Glycol Alginate	XY	X
Talc	XY	
Caffeine	XY	
Oil of Nutmeg	XY	
Sodium Tripolyphosphate	XY	
Zinc Sulfate	XY	
Lactose	XY	
Adipic Acid	XY	
Furcelleran	XY	

No final chick embryo test reports have been received, to date.
X—Tested in Rats, Mice, Hamsters and Rabbits.
XY—Tested in Rats, Mice and Hamsters.

8. A single copy of all of the above data and information is available for review in the Office of the Hearing Clerk, Food and Drug Administration, Rm. 6–88, 5600 Fishers Lane, Rockville, MD 20852, during working hours, Monday through Friday. Additional information relating to these matters will also be placed on display at this office as they become available.

Dated: July 19, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.73–15206 Filed 7–25–73;8:45 am]